Archives of Internal Medicine

VOLUME 55 MARCH 1935 NUMBER 3

RELATION OF PLASMA PROTEINS TO ASCITES AND EDEMA IN CIRRHOSIS OF THE LIVER

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In cirrhosis of the liver the accumulation of fluid in the peritoneal cavity is generally associated with a high degree of portal obstruction. This has been demonstrated repeatedly, but in a most convincing manner by McIndoe.[1] However, clinical observations suggest that other factors play important parts. The spontaneous variation of the amount of peritoneal fluid, the diminution of the ascites following the administration of diuretics and the changes subsequent to an alcoholic bout or an attack of dysentery are difficult to explain on the basis of portal obstruction alone.

Dependent edema of varying degree is frequently observed in patients with cirrhosis of the liver and portal obstruction. The edema of these patients has been explained on a basis of increased intra-abdominal pressure, causing obstruction of the venous return from the legs, or as a manifestation of cardiac failure. There are many patients concerning whom these explanations are inadequate. Edema of the dependent parts may be present in association with a minimal amount of fluid in the peritoneal cavity or without other evidence of circulatory failure. In these persons the edema commonly persists with rest in bed. It is evident that other explanations, aside from those cited, must be sought.

We have examined several other factors that contribute to the production of ascites and peripheral edema, including the blood plasma protein values, the protein content of the ascitic fluid and the effects of diets high in protein on the plasma protein levels.

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1. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, Arch. Path. **5**:23 (Jan.) 1928.

METHODS

Samples of blood were obtained repeatedly from sixteen patients with cirrhosis of the liver. In the cases in which the ascitic fluid was withdrawn for study, the specimens of blood were collected immediately preceding the abdominal paracentesis. In view of the changes in the blood plasma following paracentesis, it was necessary to withdraw the blood before rather than after abdominal tapping in order to obtain comparable conditions and results.

In addition to the patients with cirrhosis of the liver, fourteen others with various types of disease of the liver were studied for comparison.

Potassium oxalate was added to the samples of blood and ascitic fluid to prevent coagulation. The amounts of potassium oxalate were kept constant, so that variation in the values of protein as the result of the action of the oxalate on cell volume, as shown by Peters, Eisenman and Bulger,[2] would be comparable.

The plasma protein value was calculated from the protein nitrogen as determined after subtracting the nonprotein nitrogen from the total nitrogen content of the plasma. The total nitrogen content of each sample of plasma or ascitic fluid was determined in duplicate by a macro-Kjeldahl method.

The globulin of the plasma, or ascitic fluid, was precipitated by means of a buffer solution of p_H 7 of potassium di-hydrogen phosphate and di-potassium hydrogen phosphate. The nitrogen content of the filtrate was likewise determined in duplicate by the macro-Kjeldahl method. From the total nitrogen, the nonprotein nitrogen and the filtrate nitrogen were calculated the values for the albumin fraction, the globulin fraction and the albumin-globulin ratio of the plasma or ascitic fluid.

RESULTS OF THE STUDY OF THE BLOOD PLASMA PROTEINS

In the sixteen patients with cirrhosis of the liver without albuminuria, the plasma protein values were determined in forty-nine instances. The results are summarized in table 1. Fourteen patients presented the signs of uncomplicated cirrhosis of the liver; in the other two the condition was complicated by tuberculosis of the peritoneum. Fifteen had ascites, and in seven abdominal paracentesis had been done on several occasions before the studies were begun. Thirteen showed peripheral dependent edema. The diagnosis was confirmed by necropsy in seven cases.

In patient 1, neither ascites nor edema was observed, but the diagnosis was confirmed at necropsy. In patient 2, the amount of free fluid was so slight that its removal was unnecessary. Patient 10 showed massive peripheral edema and barely demonstrable ascites. An old alcoholic cirrhosis of the liver was found at autopsy. The plasma protein values were studied at frequent intervals in patients 4 and 9 during spontaneous remissions, that is, during a period when there was marked diuresis, with a decrease in the amount of ascitic fluid and peripheral edema. Later, a reaccumulation of the fluid was observed in patient 4. In another patient, the plasma protein values were studied at intervals following paracentesis. The results are summarized in table 1.

2. Peters, J. P.; Eisenman, A. J., and Bulger, H. A.: The Plasma Proteins in Relation to Blood Hydration: I. In Normal Individuals and in Miscellaneous Conditions, J. Clin. Investigation **1**:435 (June) 1925.

TABLE 1.—*Plasma Proteins in Sixteen Patients with Cirrhosis of the Liver*

Patient	Date	Total Plasma Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin-Globulin Ratio	Ascites	Jaundice	Edema	Comment
1	.....	5.7	2.45	3.25	0.754	—	+	—	Rapidly progressive; fibrinogen, 0.226 Gm. per 100 cc.; autopsy, alcoholic cirrhosis
2	.....	5.5	1.43	4.07	0.351	+	+	—	Early cirrhosis; improved with diuretics; no paracentesis
3	.....	4.6	2.21	2.39	0.923	+	+	+	Rapid course to death; no previous paracentesis; autopsy, alcoholic cirrhosis
4	10/29	5.9	2.07	3.53	0.638	+	—	+	No previous paracentesis
	2/28	5.9	1.72	4.18	0.408	+	—	+	
	3/24	5.6	....	....	.....	+	—	±	Salyrgan with good results
	4/20	6.8	2.52	4.28	0.587	+	—	—	Salyrgan with good results
	5/ 5	6.2	2.05	4.15	0.492	+	—	—	Spontaneous diuresis
	5/17	7.1	2.63	4.47	0.587	±	—	—	Diet of 180 Gm. protein daily started
	6/ 5	5.9	2.66	3.24	0.818	+	—	—	Diet of 180 Gm. protein daily continued
5	5/ 5	4.8	1.78	3.02	0.587	+	—	+	Duration of illness six weeks; two previous paracenteses
	5/14	4.8	2.11	2.69	0.785	+	—	+	
	5/28	4.6	2.07	2.53	0.818	+	—	+	
	6/ 8	4.4	2.08	2.32	0.923	+	—	+	Salyrgan; diet of 100 Gm. protein
	6/21	4.7	2.02	2.68	0.754	+	—	+	Salyrgan
	6/30	4.6	2.16	2.44	0.886	+	—	+	
	7/17	4.7	2.07	2.63	0.785	+	—	+	Fibrinogen, 0.442 Gm. per 100 cc.
	7/24	4.8	2.16	2.64	0.818	+	—	+	
	7/27	4.3	1.76	2.54	0.695	+	—	+	Diet of 100 Gm. protein continued
6	8/28	5.2	1.72	3.48	0.492	+	—	+	Several previous paracenteses; autopsy, alcoholic cirrhosis
7	2/11	4.6	1.93	2.67	0.724	+	—	+	Eight previous paracenteses
	2/23	4.8	1.78	3.02	0.587	+	—	+	
	3/ 4	4.4	1.67	2.73	0.613	+	—	+	
	3/19	4.4	1.72	2.68	0.639	+	—	+	
	3/30	4.6	1.84	2.76	0.667	+	—	+	
	4/11	4.6	1.93	2.67	0.724	+	—	+	Diet of 180 Gm. protein started before paracentesis
	4/11	4.6	1.68	2.32	0.724	+	—	+	6 hours after paracentesis
	4/12	4.1	1.64	2.46	0.667	+	—	+	18 hours after paracentesis
	4/14	4.3	1.72	2.58	0.667	+	—	+	72 hours after paracentesis
	4/21	4.4	1.80	2.60	0.695	+	—	+	
	5/ 9	4.2	1.85	2.35	0.785	+	—	+	Diet high in protein discontinued; readmission
	7/19	4.7	1.88	2.82	0.667	+	—	+	Readmission
	10/ 2	4.9	1.81	3.09	0.587	+	—	+	Readmission
	10/ 4	4.8	1.82	2.98	0.613	+	—	+	Autopsy, alcoholic cirrhosis
8	1/ 4	5.3	....	....	.....	+	+	+	No previous paracentesis
	1/29	5.8	1.62	4.18	0.388	+	±	+	Paracentesis
	2/23	5.8	1.45	4.35	0.333	+	—	+	Paracentesis; diet of 180 Gm. protein daily from 2/3
	4/ 4	5.4	1.57	3.83	0.408	+	—	+	Diet of 300 Gm. protein daily from 2/23
9	12/ 7	5.1	1.94	3.16	0.612	+	±	+	Cirrhosis present for 4 years; no paracentesis; diet of 60 Gm. protein daily
	12/15	5.9	2.36	3.54	0.667	+	—	±	Spontaneous diuresis; decrease of edema and ascitic fluid; diet of 60 Gm. protein daily
10	.....	3.8	1.90	1.90	1.000	+	—	+	No paracentesis; massive edema; autopsy, alcoholic cirrhosis, little ascites
11	.....	5.0	2.30	2.70	0.852	+	—	±	Died; no autopsy
12	.....	5.1	2.09	3.01	0.695	+	+	+	Two previous paracenteses
13	.....	5.7	1.30	4.40	0.298	+	+	+	Purpura; one previous paracentesis
14	.....	5.2	....	....	.....	+	—	+	Three previous paracenteses; autopsy, alcoholic cirrhosis
15	4/ 4	6.1	2.48	3.62	0.639	+	—	±	No previous paracentesis
	4/10	6.1	2.32	3.78	0.613	+	—	±	Autopsy, alcoholic cirrhosis; tuberculous peritonitis
16	2/10	5.7	....	....	.....	+	—	—	No previous paracentesis
	2/22	5.9	2.36	3.54	0.667	+	—	—	Cirrhosis; tuberculous peritonitis (inoculation of guinea-pigs)

From table 1 it is seen that the plasma protein values in fourteen patients were consistently below the normal level of from 6 to 8 Gm. per hundred cubic centimeters. In but five observations, and these were on plasma from two patients, was the value 6 Gm. or higher. Indeed, in five patients the determinations were constantly 5 Gm. per hundred cubic centimeters or lower. The albumin-globulin ratio was inverted. The values ranged between 0.298 and 1. The values for the albumin fraction, therefore, were low. The albumin fraction was below 2.5 Gm. per hundred cubic centimeters in every instance, except in patient 4, in whom the albumin was over 2.5 Gm., only during the period of remission.

TABLE 2.—*Plasma Proteins in Fourteen Patients with Various Disorders of the Liver*

Patient	Total Plasma Protein, Gm. per 100 Cc.	Albumin Fraction, Gm. per 100 Cc.	Globulin Fraction, Gm. per 100 Cc.	Albumin-Globulin Ratio	Comment
17	6.2	2.23	3.97	0.562	Toxic cirrhosis
18	5.8	3.71	2.09	1.778	Arsphenamine hepatitis
19	5.9	3.48	2.42	1.439	Arsphenamine hepatitis
20	6.0	2.82	3.18	0.886	Arsphenamine hepatitis
21	6.3	3.81	2.49	1.632	Catarrhal jaundice, three weeks
22	5.7	3.42	2.28	1.500	Catarrhal jaundice, ten days
23	5.9	3.44	2.46	1.500	Catarrhal jaundice, ten days
24	5.8	2.96	2.87	1.020	Catarrhal jaundice, six weeks
25	6.4	3.01	3.39	0.886	Liver and spleen enlarged; hemachromatosis (?)
26	5.5	3.30	2.20	1.500	Liver and spleen enlarged; hemachromatosis (?)
27	6.1	2.98	3.12	0.961	Liver and spleen enlarged; cirrhosis of liver (?)
28	7.9	1.58	6.32	0.250	Liver and spleen enlarged; jaundice; ascites; edema one year previously; biopsy; healed acute yellow atrophy
29	7.7	3.47	4.23	0.818	Carcinoma of colon; few metastases to liver; no edema
30	5.3	2.28	3.02	0.754	Carcinoma of stomach; metastases to liver; jaundice, ascites, edema (nutritional)

In table 2 are shown the results of determinations of the plasma proteins, albumin fraction, the globulin fraction and the albumin-globulin ratio in fourteen patients with hepatic lesions. The condition of one patient, with a history of chronic alcoholism, syphilis and arsphenamine therapy, who had a small liver, a large spleen, jaundice and ascites, was diagnosed toxic cirrhosis. The albumin-globulin ratio was inverted and the albumin fraction was correspondingly low. The plasma from three other patients with arsphenamine hepatitis was studied. The total plasma protein values were found to be near the lower limits of normal, and one patient had a low albumin content and an inverted albumin-globulin ratio.

Determinations were made on the plasma from four cases with a diagnosis of catarrhal jaundice. The total protein values were decreased. Only one of the four patients had much change in the albumin fraction. The plasma from this patient was obtained during convalescence, after a

prolonged illness. Wiener and Wiener[3] noted in catarrhal jaundice rather high plasma protein levels owing to an increase in the globulin fraction accompanied by a slight decrease in the albumin fraction.

TABLE 3.—*Proteins of Ascitic Fluid from Twelve Patients with Cirrhosis of the Liver*

Patient	Date	Total Protein, Gm. per 100 Cc.	Albumin Fraction, Gm. per 100 Cc.	Globulin Fraction, Gm. per 100 Cc.	Albumin-Globulin Ratio	Amount Removed, Liters	Specific Gravity	Total Protein Removed, Gm.	Albumin Removed, Gm.	Globulin Removed, Gm.	Number of Abdominal Paracenteses
3	.....	1.0	0.49	0.51	0.961	7.00	.....	70.0	34.30	35.70	1
4	10/29	1.5	0.71	0.79	0.886	5.75	1.012	86.2	40.82	45.42	1
5	5/ 5	0.7	0.31	0.39	0.785	4.04	1.007	28.3	12.44	15.84	3
	5/14	0.9	0.50	0.40	1.272	3.75	1.007	33.7	18.90	14.85	4
	5/28	0.8	0.43	0.37	1.173	3.80	1.008	30.4	16.40	14.00	5
	6/21	0.9	0.47	0.43	1.083	5.80	1.008	52 2	27.14	25.06	6
	7/17	1.0	0.60	0.40	1.500	4.91	.....	49.1	29.46	18.64	7
	7/27	1.0	0.54	0.46	1.173	7.41	1.007	74.0	39.96	34.04	8
6	8/ 1	0.1	....	....	.....	8.00	1.008	8.0	.....	.....	4
	8/28	0.6	....	....	.....	6.40	1.008	38.4	.....	.....	5
7	2/23	1.2	0.54	0.66	0.818	16.00	1.008	199.2	89.64	109.56	10
	3/ 4	1.0	0.47	0.53	0.886	15.00	1.004	150.0	70.50	79.50	11
	3/12	0.8	0.36	0.44	0.818	13.60	1.008	112.9	50.80	72.07	12
	3/19	0.8	0.36	0.44	0.816	14.10	1.010	114.2	51.40	62.81	13
	3/30	1.0	0.44	0.56	0.785	13.85	1.008	138.5	60.94	77.56	14
	4/11	1.3	0.60	0.70	0.852	16.00	1.012	208.0	95.68	112.32	15
	4/21	1.3	0.59	0.71	0.818	12.50	1.005	162.5	73.12	89.37	16
	5/ 9	1.4	0.67	0.73	0.923	13.50	1.008	189.0	90.72	98.28	17
	5/19	1.0	0.37	0.63	0.587	13.50	1.006	135.0	49.95	85.05	18
	5/24	0.8	0.40	0.40	1.000	7.50	1.007	60.0	30.00	30.00	19
	7/19	0.6	0.29	0.31	0.961	14.00	1.010	84.0	41.16	42.84	23
	10/ 2	0.5	0.19	0.31	0.613	12.00	1.010	60.0	22.80	37.20	28
	10/ 5	0.4	0.21	0.19	1.010	12.00	1.008	4.8	2.50	2.30	29
8	1/ 8	1.1	....	....	.....	7.20	1.002	79.2	.....	.....	1
	1/29	1.3	0.60	0.70	0.862	10.00	1.005	130.0	60.00	70.00	2
	2/22	1.3	....	....	.....	12.00	1.005	156.0	.....	.....	3
	3/14	1.7	....	....	.....	12.00	1.009	204.0	.....	.....	4
11	10/ 1	0.7	0.47	0.23	2.030	.....	.....	.....	.....	.....	1
	11/10	0.6	....	....	.....	8.00	.....	.....	.....	.....	4
12	7/27	1.3	0.69	0.61	1.128	.....	.....	.....	.....	.....	3
13	5/ 2	0.8	0.23	0.57	0.408	4.50	1.009	34.2	9.90	24.30	2
	9/14	0.7	0.39	0.31	1.220	7.60	1.005	53.2	29.30	23.90	3
14	7/16	0.9	....	....	.....	13.00	1.015	117.0	.....	.....	3
15	4/10	3.2	1.54	1.66	0.923	6.00	1.014	144.0	69.12	74.88	1*
16	2/22	4.4	2.55	1.85	1.381	8.00	1.015	352.0	205.16	147.84	1*

* Tuberculous peritonitis.

Specimens of plasma from four patients with hepatomegalia and splenomegalia, two with a clinical diagnosis of hemachromatosis, were examined. No constant observations were made, although one patient had a slightly low total plasma protein value and two patients showed a

3. Wiener, H. J., and Wiener, R. E.: Plasma Proteins, Arch. Int. Med. **46**:236 (Aug.) 1930.

slightly decreased albumin fraction with corresponding alterations in the albumin-globulin ratio. One of the four showed a much reduced albumin fraction and an increased globulin fraction in the absence of ascites or edema, but one year previously he had had jaundice, ascites and peripheral edema. Biopsy of the liver revealed healed acute yellow atrophy.

There were two patients with metastatic carcinoma of the liver. One showed but few metastases at autopsy, and during life had had no anasarca and a normal total plasma protein value with an inverted albumin-globulin ratio, the result of an increase in the globulin fraction. The second patient had a low total plasma protein value with a low albumin fraction and an inverted albumin-globulin ratio. This patient had moderately extensive anasarca; malnutrition was an important factor.

In patients with cirrhosis of the liver, the total plasma protein values were reduced. This reduction in total plasma proteins was particularly at the expense of the albumin fraction. The globulin fraction was normal or slightly increased. The albumin-globulin ratio was correspondingly inverted. In patients with less severe hepatic damage the plasma protein determinations showed less marked alterations. The values for total plasma proteins were either normal or slightly reduced. The albumin fraction was occasionally below the lower normal values. The globulin fraction was frequently increased.

RESULTS OF THE STUDY OF THE ASCITIC FLUID

The protein content of thirty-five samples of ascitic fluid removed from the twelve patients on whom plasma protein studies were made are summarized in table 3. The total protein values, albumin fraction, globulin fraction and albumin-globulin ratio were determined. Also, the loss of protein, albumin and globulin was calculated from the amount of ascitic fluid removed by paracentesis. The fluid from two patients who had tuberculous peritonitis complicating hepatic cirrhosis contained 3.2 and 4.4 Gm. of protein per hundred cubic centimeters. The total protein content of the fluid of patients with uncomplicated hepatic cirrhosis varied between 0.1 and 1.7 Gm. per hundred cubic centimeters. The values obtained in these samples of ascitic fluid are in agreement with the findings of Loeb, Atchley and Palmer,[4] Foord, Youngberg and Wetmore[5] and Barnett, Jones and Cohn.[6] The loss of protein as a result

4. Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: On the Equilibrium Condition Between Blood Serum and Serous Cavity Fluids, J. Gen. Physiol. **4**:591, 1922.

5. Foord, A. G.; Youngberg, G. E., and Wetmore, V.: The Chemistry and Cytology of Serous Fluids, J. Lab. & Clin. Med. **14**:417 (Feb.) 1929.

6. Barnett, C. W.; Jones, R. B., and Cohn, R. B.: The Maintenance of a Normal Plasma Protein Concentration in Spite of Repeated Protein Loss by Bleeding, J. Exper. Med. **55**:683 (May) 1933.

of abdominal paracentesis in patients with uncomplicated cirrhosis of the liver was occasionally found to exceed 200 Gm. at one time. The average calculated daily loss for the patients repeatedly studied was usually less than 10 Gm., but occasionally was as much as 18 Gm.

The albumin-globulin ratios were found to vary within wide limits. The albumin-globulin ratio of the proteins of the fluid consistently was higher than that of the corresponding plasma proteins. A larger proportion of the albumin fraction than of the globulin fraction had passed into the ascitic fluid.

In summary, the ascitic fluid removed from patients with uncomplicated cirrhosis of the liver contained from 0.1 to 1.7 Gm. of protein per hundred cubic centimeters. The albumin fraction of the proteins of the ascitic fluid was relatively greater than that of the plasma proteins; that is, the albumin-globulin ratio of the proteins of the ascitic fluids was higher than that of the plasma proteins.

EFFECT OF PROTEIN FEEDING ON THE PLASMA PROTEINS

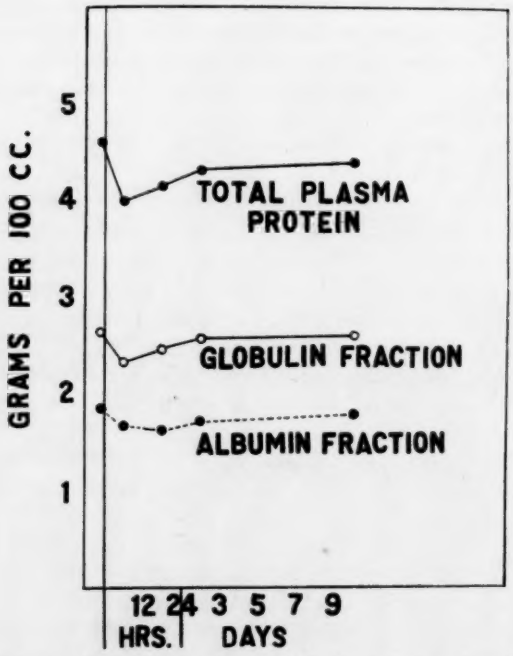
In an effort to determine whether the blood plasma proteins could be increased by a diet high in protein, food containing large amounts of protein was given to four patients. Patient 4 showed a decrease in the plasma proteins during a period of two weeks while ingesting 180 Gm. of protein a day. During two weeks preceding the diet high in protein, the patient had had spontaneous diuresis with a resultant decrease of ascites and edema. The relationship between the fluid intake and urinary output was reversed within a few days after the diet high in protein was started. Patient 5 was unable to eat all the protein food offered because of anorexia. Patient 7 received food containing 180 Gm. of protein daily for four weeks. The diet was well taken.

No effect on the plasma protein content was demonstrated, such as is usually observed when diets high in protein are given patients with hypoproteinemia resulting from dietary deficiency; indeed, in this case, the total plasma protein content fell from 4.6 to 4.2 Gm. per hundred cubic centimeters during the period of forced feeding of protein. Patient 8 received a diet which contained approximately 180 Gm. of protein daily for three weeks. There was no essential change in the plasma protein values. For the following six weeks, 300 Gm. of protein was ingested daily. There was a slight decrease in the globulin fraction of the plasma proteins. From the observations on these few patients the hypoproteinemia of hepatic cirrhosis does not seem to be a result of dietary deficiency. Experiments on nitrogen balance were not carried out to determine the proportion of ingested protein which was digested and absorbed. There was no excess of undigested meat fibers in the stools. The determination of the nitrogen content of the stools was carried out

in patient 8 during the periods when 180 Gm. and 300 Gm. of protein were ingested. The daily loss of nitrogen in the stools was 1.26 and 1.16 Gm. per day, respectively.

IMMEDIATE EFFECT OF ABDOMINAL PARACENTESIS ON THE PLASMA PROTEIN VALUES

It was repeatedly noted, even by the patient, that an appreciable decrease in the peripheral edema and marked diuresis took place following the removal of ascitic fluid. The plasma protein values were determined at intervals following paracentesis in patient 7. The changes are shown in the figure and are recorded in table 1. As noted previously by Bernard,[7] there was a profound disturbance in the water metabolism. The albumin and globulin fractions were reduced proportionately at



Changes in the plasma proteins following the removal of ascitic fluid in patient 7.

7. Bernard, E.: Dilution et concentration sanguines après les ponctions d'ascites: L'étape sanguine de la fonte des oedèmes, Semaine d. hôp. de Paris **6**:581 (Dec. 15) 1930.

first. Later, the globulin fraction of the plasma rose and did so more rapidly than the albumin fraction. Thus, following paracentesis there may be diuresis accompanied by further reduction of the total protein value of the serum, possibly due to dilution of the blood plasma.

COMMENT

From our observations it is evident that a considerable number of patients with cirrhosis of the liver show a definite decrease in the total plasma proteins. The albumin fraction was consistently decreased, and the albumin-globulin ratio was inverted. These observations are in accord with those of others.[8] It was also clear that the patients with peripheral edema as well as ascites commonly showed a decrease in the total plasma proteins, showing that this factor was of importance in explaining the presence of peripheral edema.

In seeking an explanation for the low plasma protein values in these cases, three factors were considered: an inadequate intake or absorption of protein, defective formation of plasma proteins and a loss of protein from the blood stream into the ascitic fluid.

To test whether an inadequate intake or absorption of protein was responsible for the low plasma protein content, four patients were given large amounts of protein, from 100 to 300 Gm. a day, but it was impossible to increase the proteins of the blood. While malnutrition may play a part in some patients with cirrhosis, this did not seem to be the case, at least in the four patients who were given diets liberal in protein. Although studies of the nitrogen balance were not made, observation suggested no loss of ingested proteins in stools. When there is prolonged decreased protein intake, the addition of liberal amounts of protein to the diet causes an increase of the blood proteins. In the cases of cirrhosis, the plasma proteins were not increased as a result of available dietary proteins. It was manifest then that an inadequate intake could not explain our observations. The other two factors, namely, defective formation and loss of protein from the blood stream into the ascitic fluid, were of more importance.

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8. (*a*) Gilbert, A., and Cheray, M.: Diminution des substances albumineuses du sérum sanguin chez les cirrhotiques ascitiques, Mém. Soc. de biol. **63**:487, 1907. (*b*) Grenet, H.: Diminution des albumines du sérum sanguin chez les hépatiques, Mém. Soc. de biol. **63**:532, 1907. (*c*) Salvesen, H. A.: Variations in the Plasma Proteins in Nonrenal Conditions, Acta med. Scandinav. **72**:113, 1929. (*d*) Abrami, P., and Robert-Wallech: Modifications du sérum sanguin du foie avec ascites: Inversion du rapport sérums-globulines, Compt. rend. Soc. de biol. **101**:291 (May 25) 1929. (*e*) Peters, J. F., and Eisenman, A. J.: The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, Am. J. M. Sc. **186**:808 (Dec.) 1933. (*f*) Wiener and Wiener.[3] (*g*) Barnett, Jones and Cohn.[6]

Thompson, Ziegler and McQuarrie [9] and Myers and Taylor [10] have indicated that hypoproteinemia may develop as a result of defective formation of blood proteins. That this mechanism is of importance in cirrhosis of the liver is suggested by two observations: first, our inability to raise the level of the blood proteins by high protein feeding and, second, the fact that the blood protein may be decreased in disease of the liver without ascites or edema. This explanation also has been suggested by Grenet,[8b] Jollis [11] and Salvesen.[8c] It has been shown by Sawada [12] that following hepatic damage in rabbits there is a decrease in the serum albumin and fibrinogen and an increase in serum globulin. We found that patients with limited cirrhosis showed a decrease in the serum albumin and a slight increase in the serum globulin. In patients with more extensive cirrhosis, the albumin fraction was considerably decreased, and the globulin fraction was approximately normal.

There remains for discussion the factor of the loss of protein into the ascitic fluid. We have said that this protein was relatively rich in albumin. The total amount of protein in the ascitic fluid was, in many cases, considerable. In some instances, as much as 200 Gm. was removed at one time, and in a few cases the daily calculated loss was as much as 18 Gm. of protein.

The removal of a comparable amount of protein from dogs by plasmaphoresis results in only transient hypoproteinemia. For example, Barnett, Jones and Cohn [6] found that the removal of 5.2 Gm., or 0.41 Gm. of protein per kilogram of body weight, from a dog every day for six weeks failed to produce a deficiency of plasma protein.

In the cases we observed, repeated abdominal paracentesis with the loss of large amounts of protein did not lead to a progressive decrease in the total plasma protein or in the albumin or globulin fraction. In spite of this loss and high protein feeding, the plasma proteins were maintained at a low level. This state of affairs is not reproduced in the dog, in which the loss is accompanied by protein feeding.

From what has been said, it seems justifiable to conclude that the low plasma protein values in cirrhosis of the liver are the result of the loss of protein into the ascitic fluid together with defective formation of plasma proteins. In most instances a diet low in protein and a lack of absorption are not contributing factors. The ascites, then, would

9. Thompson, W. H.; Ziegler, M., and McQuarrie, I.: A Comparative Study of the Inorganic Metabolism in Nephrosis and in Edema of Undetermined Origin, Am. J. Dis. Child. **44**:650 (Sept.) 1932.

10. Myers, W. K., and Taylor, F. H. L.: Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins, J. A. M. A. **101**:198 (July 15) 1933.

11. Jollis, quoted by Grenet.[8b]

12. Sawada, T.: Biochemical Investigation of the Blood in Cases of Experimental Disturbance of Liver Function, Jap. J. Gastroenterol. **3**:38 (April) 1931.

appear to result from increased hydrostatic pressure in the portal vein and a low plasma protein level. The dependent edema can be explained in part by the presence of the low blood plasma protein content and increased venous pressure. The latter can occur only in the presence of massive ascites.

SUMMARY

Sixteen cases of cirrhosis of the liver were studied. A deficiency in the total plasma protein was found. The decrease was most pronounced in the albumin fraction. The albumin-globulin ratio was inverted.

Similar but less extensive and less consistent alterations in the plasma protein values were observed in fourteen cases of other forms of disease of the liver.

In patients with cirrhosis of the liver the following conditions were observed:

1. The protein content of ascitic fluid varied between 0.1 and 1.7 Gm. per hundred cubic centimeters. The albumin content of the ascitic fluid was proportionately greater than that of the blood plasma.

2. The removal of ascitic fluid gave rise to changes in the plasma protein value and a temporary hydremia with corresponding diuresis.

3. Peripheral edema without circulatory failure was associated with a reduction of the plasma proteins.

In cirrhosis of the liver the appearance of ascites must depend somewhat on the osmotic pressure of the blood plasma as well as on portal obstruction. The hypoproteinemia may arise from a defective formation of plasma proteins and a loss of protein into the ascitic fluid. The defect may be due to alteration in the function of the liver.

NITROGEN AND SULPHUR METABOLISM IN BRIGHT'S DISEASE

VI. EFFECT OF DIETS LOW IN SULPHUR ON THE EXCRETION OF SULPHUR

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These studies were initiated in the attempt to utilize the effects of iodides and salicylates on the excretion of nitrogen and sulphur [1] in the study of Bright's disease. It has been shown previously that iodides and salicylates mobilize different types of nitrogen and that the effect of iodide is produced by the mediation of the thyroid gland.[2] When an attempt was made to conduct similar studies on patients with renal disease, it was observed that patients with the nephrosis syndrome showed a relationship between the amount of nitrogen and the amount of sulphur excreted in the urine similar to that exhibited by persons as an effect of the administration of iodides, whereas patients with other types of renal disease showed a totally opposed relationship between these two urinary constituents. Further studies indicated that the reaction to iodides and salicylates in patients with Bright's disease [3] was different from that exhibited by normal persons, but owing to a variety of factors the results were not sufficiently regular to warrant statistical comparison.

In brief, patients with edema of renal origin tend to retain sulphur [4] to an even greater extent than nitrogen, whereas patients without renal

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From the medical clinic of the Peter Bent Brigham Hospital.

This work was aided by a grant from the Proctor Fund for the Study of Chronic Diseases of Harvard University.

1. Grabfield, G. P.: The Action of Iodides on the Nitrogen Metabolism, Boston M. & S. J. **197**:1121, 1927. Grabfield, G. P., and Knapp, E.: The Effect of Salicylates on the Nitrogen Metabolism with Special Reference to the Effect of the Cation of the Salt, J. Pharmacol. & Exper. Therap. **32**:341, 1928.

2. Grabfield, G. P.; Flower, B.; Gray, C., and Knapp, E.: The Mechanism of the Action of Iodides on the Nitrogen Metabolism, J. Clin. Investigation **4**:323, 1927.

3. Grabfield, G. P.: The Effect of Iodides on the Nitrogen and Sulphur Metabolism in Bright's Disease, J. Pharmacol. & Exper. Therap. **42**:253, 1931.

4. Grabfield, G. P.: Studies on the Nitrogen and Sulphur Metabolism in Bright's Disease: I. Retention of Nitrogen and Sulphur in "Nephrosis," J. Clin. Investigation **9**:311, 1930.

edema tend to have a negative sulphur balance.[5] Whether the opposing behavior of the excretion of sulphur in the two types of nephritis is a part of the same mechanism, we have so far been unable to determine. It is obvious, however, that some special mechanism is at work, because the content of nonprotein constituents of the blood under the two sets of circumstances would lead one to suspect that the reverse would occur. Wakefield and Keith,[6] Wakefield,[7] Loeb and Benedict [8] and others have shown that the patient in whom the metabolic sulphur balance becomes negative may, and frequently does, have a high level of inorganic sulphate in the protein-free blood filtrate, whereas Keith has shown that the content of inorganic sulphate in patients with the nephrosis syndrome tends to be low, like the content of blood urea. That this behavior of the sulphur is a special mechanism present in Bright's disease and is not associated merely with edema has been shown by the study of a patient with edema of unknown, but nonrenal, origin who had a persistent negative sulphur balance.[9]

It was the object of the present study to find a method of varying the intake of sulphur independent of the intake of nitrogen. In considering methods of accomplishing this, we decided not to attempt to increase the sulphur intake by feeding products containing sulphur, because this will constitute a special problem to be considered in another group of experiments. On the other hand, the use of gelatin enabled us to diminish the intake of sulphur without varying the intake of nitrogen, and we were able in that way to reduce the intake of sulphur to about 100 mg. a day. The feeding of gelatin has the obvious disadvantage that it is an incomplete protein and cannot provide completely for the needs of the body. It is evident from Robison's figures [10] and from his extensive study of the biologic value of various proteins [11] that gelatin can be used only partly to provide the protein in protein-free diets. It may be, therefore, that in these experiments the factor of

5. Grabfield, G. P.: Studies on the Nitrogen and Sulphur Metabolism in "Bright's Disease": II. Observations on the Nitrogen and Sulphur Excretion in Patients without Renal Edema, J. Clin. Investigation **10**:309, 1931.

6. Wakefield, E. G., and Keith, N. M.: A Study of Inorganic Sulphates in Relation to Acid-Base Equilibrium in Renal Insufficiency and "Renal Acidosis," J. Clin. Investigation **9**:19 (Aug.) 1930.

7. Wakefield, E. G.: Inorganic Sulphates in Renal Insufficiency, Arch. Int. Med. **44**:244 (Aug.) 1929.

8. Loeb, R. F., and Benedict, E. M.: Inorganic Sulphates in Human Blood, J. Clin. Investigation **4**:33, 1927.

9. Grabfield, G. P.; Driscoll, M., and Gray, M. G.: Nitrogen and Sulphur Metabolism in Bright's Disease: V. Metabolic Study of a Patient with Edema of Unknown Origin, Arch. Int. Med. **54**:764 (Nov.) 1934.

10. Robison, R.: Gelatine as a Food Stuff, Biochem. J. **16**:111, 1922.

11. Robison, R., and Martin, C. J.: On the Biological Value of Certain Proteins, Biochem. J. **16**:407, 1922.

protein starvation must be taken into account, but, in any case, the starvation was complete only so far as the sulphur was concerned. In our experiments the nitrogen balance reacted in a manner similar to that of Robison's normal subjects.

We used three day periods in order to make our results comparable with those of our previous experiments and because our experience showed that sick patients cannot tolerate the somewhat unpleasant diet of gelatin for a longer period. While such a period is short, it yields results that are interpretable. The patients were fed whatever diet seemed appropriate from a therapeutic point of view. After the excretion reached a level all the protein in the food was provided by gelatin for a three day period, the caloric and nitrogen value of the diet remaining unchanged. The diet was carefully weighed, and the food refused was weighed. The water in the food was taken into account, and the intake of fluid was adjusted so that the total intake of fluid amounted to 2,500 cc. per day. The patients were all in bed, and the caloric value of the diet was from 1,500 to 2,000 per day. We studied three consecutive three day periods, and the studies included examination of the total nitrogen, the total sulphur and the creatinine of the urine. Analysis of the feces was not done for technical reasons, and it has been found that no material information is added by such analyses.[12]

Unfortunately, the available patients formed a rather mixed group; consequently it is probably best to consider each one separately. For control observations we studied two patients (cases 13 and 14) who had good renal function and whose chief difficulty was hypertension. Neither had edema during the period of study; in neither case was the serum protein determined, because it was not considered that it was lowered. Table 1 shows the effect of the gelatin diet in these patients, and shows only a slight attempt to reduce the excretion of sulphur in response to the low intake of sulphur. We were particularly anxious to use these patients because Robison, in his careful studies, was unable to publish his figures on sulphur,[13] and these patients may in a sense be taken as normal controls. There was a definite but very slight tendency to a reduction in the excretion of sulphur in response to the sulphur-poor diet. Both patients used for controls showed diuresis during the gelatin feeding, which tended to increase the urinary excretion of sulphur.[14] However, the negative sulphur balance during the period of the gelatin diet amounted to 700 mg. on the average.

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12. Grabfield, G. P.: Unpublished data.

13. Robison, R.: Personal communication to the authors.

14. Fowler, C. C., and Hawk, P. B.: Studies on Water Drinking: II. The Metabolic Influence of Copious Water Drinking with Meals, J. Exper. Med. **12**: 388, 1910.

Case 10 may be considered with this group, because, although the patient had advanced renal disease and at times had a negative sulphur balance, the serum protein values were at all times normal. It will be seen (table 1) that in him also the excretion of sulphur was diminished only slightly while he was on the diet low in sulphur. The nitrogen level of his diet was low, and as he was very sick he was unable to eat the diet as well as the other patients.

TABLE 1.—*The Intake and Urinary Output of Sulphur and Nitrogen for Patients with Normal Serum Protein Values*

Case	Day	Sulphur, Cg.		Nitrogen, Gm.	
		Intake	Output	Intake	Output
10	1	38	63*	3.6	4.1*
	2	41	82	4.5	3.5
	3	44	39	4.3	3.3
	4	4	37	2.8	1.7
	5	3	78	1.8	4.4
	6	4	42	1.5	2.4
	7	40	46	4.5	2.5
	8	42	47	4.5	4.1
	9	46	52	4.5	4.2
17	1	84	64	9.7	8.4
	2	64	45	7.6	7.3
	3	72	47	8.5	7.4
	4	12	45	9.6	8.2
	5	12	37	8.5	7.7
	6	12	35	9.7	6.2
	7	81	42	9.6	7.5
	8	83	54	9.7	8.1
18	2	65	42	8.4	5.9
	3	64	41	8.8	5.4
	4	11	37	9.1	6.3
	5	15	33	9.6	6.6
	6	12	28	9.3	6.7
	7	62	37	8.2	6.8
	8	67	32	8.8	4.8

* This figure was corrected from data on the excretion of creatinine.

Thus, in three patients with normal serum protein levels the response to gelatin feeding was a slight diminution in the urinary excretion of sulphur and a slight increase in the urinary excretion of nitrogen. These patients showed an average negative sulphur balance of 760 mg. during the period of gelatin feeding (chart 1, upper columns).

The remaining patients studied had one factor in common in that they all showed some degree of depletion of serum proteins. All showed also evidence of glomerular lesions. With one exception, there was a strong tendency toward diminution of the excretion of sulphur in response to the diet low in sulphur. As the patients were all receiving the same amount of protein, about 60 Gm., it is proper to consider them

together (table 2). The nitrogen balance was close, with two patients exhibiting a strong tendency toward a negative balance in certain instances. In two cases the experiments coincided with the disappearance of edema. Only in case 14 was the albumin-globulin ratio reversed (table 3), although it was low in the other cases. It is to be noted that in each patient there was a strongly positive sulphur balance before the

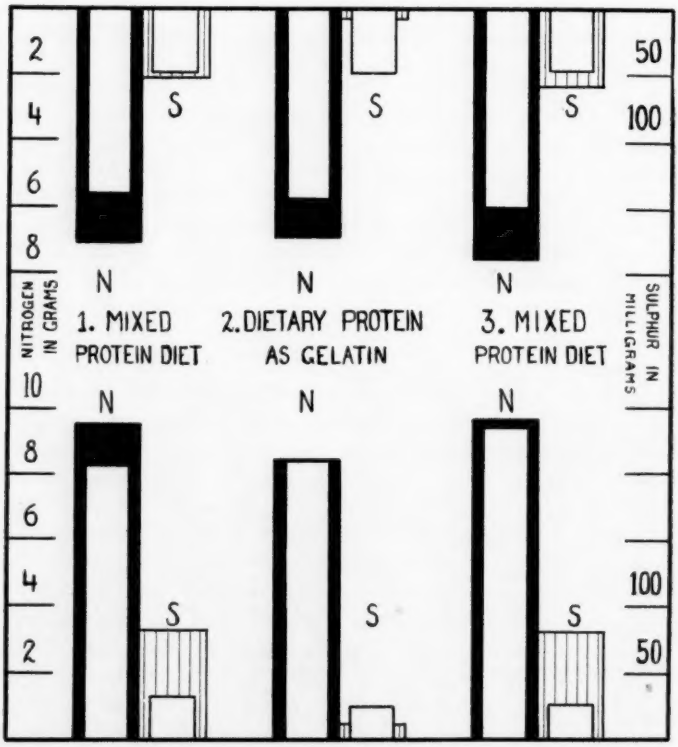

Chart 1.—The upper columns show the average daily intake of nitrogen and sulphur and the urinary output for patients with normal serum protein values. The lower columns show the daily intake of nitrogen and sulphur and the urinary output for patients with depleted serum protein values. The solid or shaded columns represent the intake, the clear columns, the output. The middle of each indicates the period of the gelatin diet. Note the strongly positive sulphur balance shown in the lower columns and compare the slightly negative balance in this group during the period of gelatin feeding with the strongly negative balance shown in the upper columns.

TABLE 2.—*The Intake and Urinary Output of Sulphur and Nitrogen of Patients with Chronic Nephritis with Depleted Serum Protein Values*

Case	Day	Sulphur, Cg.		Nitrogen, Gm.	
		Intake	Output	Intake	Output
13	1	81	24	9.6	5.9
	2	80	20	9.5	5.1
	3	81	19	9.5	7.0
	4	13	33	9.6	7.8
	5	12	17	8.0	6.2
	6	12	14	7.3	5.2
	7	77	11	9.0	4.8
14	1	77	45	9.3	7.1
	2	82	37	9.6	11.8
	3	80	49	9.6	11.2
	4	10	14	5.6	5.4
	5	11	30	6.5	11.0
	6	12	17	7.8	6.2
	7	85	22	9.6	7.9
	8	77	39	9.5	9.6
	9	79	27	9.3	5.1
15	1	81	27	9.3	9.5
	2	81	43	8.5	10.0
	3	76	29	8.4	9.9
	4	10	32	9.4	10.5
	5	12	25	9.4	9.2
	6	14	27	9.6	10.8
	7	80	19	9.5	10.5
	8	77	33	8.4	12.0
	9	86	25	9.5	12.7
16	1	79	27*	9.6	8.3*
	2	81	24	9.3	8.2
	3	81	29	9.7	8.9
	4	12	26	9.1	10.0
	5	13	32	9.7	10.5
	6	13	32	9.7	9.9
	7	86	31	9.7	11.5
	8	81	27	9.7	8.9
	9	84	32	9.7	9.1

* This figure was corrected from data on the excretion of creatinine.

TABLE 3.—*Laboratory Data During the Period of Study*

Case	Date	Blood Urea Nitrogen, Mg. per 100 Cc.	Blood Creatinine, Mg. per 100 Cc.	Blood Cholesterol, Mg. per 100 Cc.	Blood Sodium Chloride, Mg. per 100 Cc.	Excretion of Phenolsulphonphthalein, per Cent	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent
10	10/10	32	...	...	...	5	...	...	...
	10/14 to 1/10	27 to 50	...	...	...	10 to 15	...	...	...
	11/ 7	..	...	...	...	..	7.6	5.0	2.6
13	12/19	..	...	...	...	52	...	...	...
	12/22	13	...	...	...	..	...	...	...
14	10/21	..	...	...	...	45	...	...	...
15	11/13	20	...	...	...	..	...	...	...
	11/15	..	...	...	...	20	...	...	...
	12/ 4	20	...	382	483	..	5.6	3.9	1.7
16	3/ 2	..	...	...	...	78	...	...	...
	3/ 6	10	...	411	450	..	4.6	2.1	2.5
	3/12	7	...	235	462	66	5.0	2.4	2.6
17	12/14	43	7.5	360	...	..	5.1	3.0	2.1
	12/17	52	...	...	...	..	...	...	...
	12/22	43	...	310	...	..	4.8	3.0	1.8
18	10/30	..	5.0	355	...	..	4.6	2.5	2.0
	11/ 9	54	...	...	...	..	...	...	...
	11/16	28	2.9	370	...	..	4.3	2.7	1.6
	11/18	..	...	...	...	10	...	...	...

ingestion of the gelatin diet and that despite this the amount of sulphur excreted when little sulphur was given tended to be lower than in the patients with normal serum protein values. Whereas the first group of patients lost, on the average, 0.76 Gm. of sulphur during the gelatin feeding and the two normal controls lost 700 mg., the patients with low total serum protein values lost, on the average, only 400 mg. This can be shown also by comparing the nitrogen-sulphur ratios of the two groups (chart 2).

These experiments demonstrate no new fact but provide added evidence that the depletion of the serum proteins in Bright's disease is associated with the necessity of retention of sulphur in the organism. Further experiments are in progress to determine the fate of the retained sulphur.

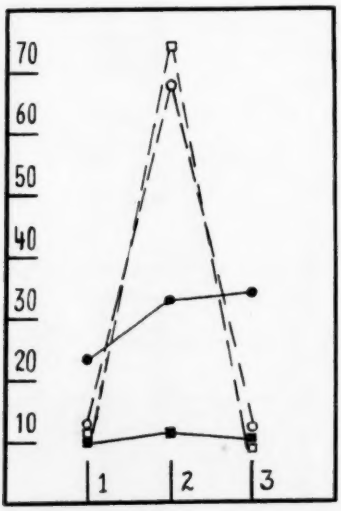

Chart 2.—The nitrogen-sulphur ratios shown in chart 1. The broken lines connect the nitrogen-sulphur ratios of the intake, and the solid lines and solid figures, the ratios of the output. The squares respresent the ratio in the urine of patients with normal serum protein values, and the circles, that of those with depleted serum protein values. Note the rise in the nitrogen-sulphur ratio in the patients with depleted serum protein values, indicating the effort to retain sulphur.

SUMMARY AND CONCLUSIONS

We have reported the effect of diets low in sulphur in seven patients. Three had normal serum protein values, and in four the values were low. The latter four had Bright's disease. The experiments showed that in patients with Bright's disease and low serum protein values the excre-

tion of sulphur tends to diminish to a greater extent than in patients with normal serum protein values when diets low in sulphur are given.

REPORT OF CASES

CASE 10.—A white man, aged 35, was admitted to the hospital on Sept. 28, 1929, with a complaint of headache and vomiting. He was known to have had "kidney trouble" since 1908, when his feet and legs were swollen for a month. About a year prior to admission he noticed a feeling of ill health and an increase in the number of headaches. Vomiting became more severe and of longer duration until in the preceding four months it occurred almost constantly. Eight years before, he had an attack of so-called infantile paralysis, with almost complete bilateral facial paralysis and only slight symptoms in the arms and legs. The facial paralysis lasted for six months. Physical examination revealed a slightly enlarged heart and hemorrhagic retinitis. The blood pressure was 182 systolic and 110 diastolic. Only a trace of phenolsulphonphthalein was excreted. The blood count showed: hemoglobin content, 30 per cent, and red cells, 3,200,000. The blood urea nitrogen was 52 mg. per hundred cubic centimeters. The basal metabolic rate was minus 3 per cent. The patient improved symptomatically. Urinalysis revealed a low specific gravity, a slight trace of albumin and no formed elements of importance in the sediment. On October 10, the excretion of phenolsulphonphthalein was less than 5 per cent; the blood urea nitrogen was 32 mg.; the hemoglobin content was 50 per cent, and the red blood cell count was 3,750,000. On October 14, the blood urea nitrogen was again 53 mg., and the urine showed a slight trace of albumin and many coarsely granular casts. The blood urea nitrogen varied from 50 to 27 mg., and the excretion of phenolsulphonphthalein ranged between 10 and 15 per cent. By October 31 red blood cells had appeared in the sediment, and these persisted. On November 7 the total blood protein was 7.6 per cent; the albumin, 5 per cent, and the globulin, 2.6 per cent. He was discharged, and was readmitted in January 1930. On April 22, 1930, he died of uremia, with the blood urea nitrogen 273 mg. At autopsy the right kidney was found to be contracted, weighing only 60 Gm., and the left kidney was almost entirely replaced by a cystic degeneration.

CASE 13.—A white woman, aged 66, was admitted to the hospital on Dec. 18, 1930, with a complaint of palpitation and fainting spells for fifteen years. She was observed in the outdoor department during this period, and constantly exhibited hypertension without evidence of renal disease. However, she had cardiac insufficiency and, for a number of years, auricular fibrillation. She was treated with digitalis, and her blood pressure was 250 systolic and 110 diastolic on admission. She was admitted to the hospital for rest in bed and for further study. On admission the basal metabolic rate was plus 25 per cent; the hemoglobin content was 83 per cent, and the red blood cell count was 5,500,000. The patient's heart was definitely enlarged and fibrillating, but there were no significant murmurs. Her stay in the hospital was uneventful, and she was discharged on Jan. 17, 1931, improved, without much change in the blood pressure. The excretion of phenolsulphonphthalein on December 19 was 52 per cent, and on December 22 the blood urea nitrogen was 13 mg. per hundred cubic centimeters. The urine showed the slightest possible trace of albumin on a few occasions and occasionally some hyaline casts. Subsequent to her discharge the patient followed the expected course and died on Oct. 9, 1932, without giving evidence of renal failure.

CASE 14.—A white woman, aged 65, was admitted to the hospital on Oct. 20, 1930. She had been observed in our clinic since 1923, having had hypertension since that time. Her chief complaint was palpitation and dyspnea on exertion. On entrance the blood pressure was 230 systolic and 110 diastolic. There was moderate enlargement of the heart, but no evidence of congestive failure. The hemoglobin was 75 per cent, and the red blood cell count was 4,750,000. There was no evidence of retinal sclerosis, but moderate sclerosis of the peripheral arteries was present. The basal metabolic rate was plus 4 per cent. On October 21 the excretion of phenolsulphonphthalein was 45 per cent. During her stay in the hospital, her blood pressure gradually fell to 180 systolic and 90 diastolic. At times the urine showed a few red cells and rare finely granular casts, and occasionally there was the slightest possible trace of albumin. The patient had no edema and was discharged improved on Dec. 16, 1930.

CASE 15.—A white married women, aged 58, was admitted to the hospital on Nov. 12, 1930. In 1917 albuminuria and a few casts appeared in the urine following lobar pneumonia and an abscess of the lung. For the next ten years her renal function remained good. The excretion of phenolsulphonphthalein was above 40 per cent on various occasions. In 1928 she began to complain of dizziness and headache. She then showed hypertension, the pressure being 215 systolic and 110 diastolic. The heart was slightly enlarged, and the urine showed a trace of albumin and numerous casts. In April 1929, she had an acute attack of pyelitis, with fever and chills. Her blood pressure fell to 145 systolic and 64 diastolic during this period, and the blood urea nitrogen rose to 39 mg. per hundred cubic centimeters during the acute illness, but fell to 17 mg. as she improved. There were no casts in the urine, but there was some edema. During the entire period she had mild diabetes, which was readily controlled by diet. In November 1929 she returned to the hospital. The blood pressure was 204 systolic and 98 diastolic; the blood urea nitrogen was 8.6 mg.; the blood sugar was 149 mg., and the excretion of phenolsulphonphthalein was 25 per cent. After that, the urine always showed a large trace of albumin and a slight trace of sugar. The blood pressure remained around 240 systolic and 120 diastolic. Six weeks before the last admission she complained of drowsiness; this was observed at the time she was admitted. On admission the blood pressure was 220 systolic and 129 diastolic, and the blood sugar was 194 mg. Her heart was enlarged, and there was slight pitting edema. The hemoglobin content was 60 per cent; the red blood cell count, 3,800,000; the blood urea nitrogen, 20 mg. per hundred cubic centimeters, and the excretion of phenolsulphonphthalein, 20 per cent. She improved rapidly, and there was no demonstrable edema during the period of the experimental study. Digitalis was given throughout her stay in the hospital. During the entire period the specific gravity of the urine varied between 1.007 and 1.014, and the urine constantly showed a trace of albumin, the slightest possible trace of sugar and occasional casts. The patient was discharged on Dec. 9, 1930, much improved.

CASE 16.—A white woman, aged 18, was admitted to the hospital on Feb. 7, 1931, with a complaint of edema of the ankles of six weeks' duration following an infection of the upper respiratory tract. Her history revealed that she noticed a slight swelling of each ankle one year before admission, but that she had felt well. On admission, physical examination revealed a white spot in one retina and one small, old hemorrhage in the other. There was moderate enlargement of the thyroid isthmus, and the blood pressure was 132 systolic and 82 diastolic. There

was distinct pitting edema of the legs which disappeared over night. She was essentially symptom-free throughout her stay. Her basal metabolic rate was plus 5 per cent. The hemoglobin content was 80 per cent, and the red blood cell count was 4,000,000. On March 10 there was slight pitting edema which soon disappeared. The excretion of phenolsulphonphthalein was between 66 and 80 per cent; the blood urea nitrogen varied from 7 to 14 mg. per hundred cubic centimeters, and the blood cholesterol was 416 mg. per hundred cubic centimeters. The total blood protein was 4.8 per cent, the albumin was 2 per cent and the globulin, 2.8 per cent. The urine showed from a slight trace to a trace of albumin throughout her stay, and, rarely, red blood cells and occasional casts. The middle of March the blood protein content began to rise. By April 16 the blood protein value was normal and the cholesterol concentration had fallen. She was discharged, much improved, May 3.

CASE 17.—A white man, aged 24, was admitted to the hospital on Dec. 10, 1931, complaining of blurred vision and headache. His history showed that in 1927 he first noticed generalized edema; at that time a large amount of albumin and some casts were found in the urine, but there was no hypertension. He was given a diet high in protein and was considered to have passed through the nephrosis syndrome. He was followed up in the outdoor department after his discharge. He felt fairly well for a few months, although he continued to have some edema. Headache and dimness of vision persisted, and there gradually developed hypertension, which on the last admission was 170 systolic and 110 diastolic. On this admission there was secondary anemia, the red blood cell count being 3,900,000; the blood urea nitrogen was 51 mg., and the excretion of phenolsulphonphthalein, 2 per cent. He had no edema and had had none for a year. There were marked retinal arteriosclerosis and some cardiac enlargement. The urine showed a large amount of albumin, an occasional granular and hyaline cast and a good many red cells. He complained of blurred vision and headache, weakness and occasional twitching. The blood protein value was slightly lowered, the total protein being 5.1 per cent, the albumin, 3 per cent, the globulin, 2.1 per cent, the cholesterol, 360 mg. per hundred cubic centimeters, and the creatinine, 7.5 mg. per hundred cubic centimeters. By January 4, the blood creatinine had fallen to 3 mg., but the excretion of phenolsulphonphthalein amounted to only a trace. The blood urea nitrogen remained at about the same level, and symptomatically he was relieved. He was discharged on Jan. 17, 1932.

CASE 18.—A white woman, aged 20, was admitted to the hospital on Oct. 29, 1931, complaining of edema. Her history showed scarlet fever in infancy and diphtheria at the age of 4 years. In 1927 she sprained an ankle and both ankles, the legs and the face began to swell. At that time she was admitted to the outdoor department, where she has been followed since. Her blood pressure at that time was 147 systolic and 90 diastolic, and there was a large amount of albumin in the urine as well as a moderate number of casts. She had secondary anemia; the specific gravity of the urine was 1.010, and the reaction was constantly alkaline. Increasing hypertrophy of the heart was noticed; the blood urea nitrogen was 27 mg., and the excretion of phenolsulphonphthalein was 25 per cent and later 17 per cent. She was given a salt-free diet low in protein and remained fairly well until September 1931, when a cold caused an increase in the edema. Headache became a troublesome symptom, and the blood pressure rose to 174

systolic and 100 diastolic. On admission to the hospital her blood pressure was 190 systolic and 110 diastolic; the red blood cell count was 2,950,000; the hemoglobin count, 55 per cent, and the blood urea nitrogen, 33 mg. The excretion of phenolsulphonphthalein had fallen to 10 per cent on admission. The total protein was 4.6 per cent, the albumin, 2.5 per cent, the globulin, 2 per cent, the creatinine, 5 mg. and the cholesterol, 355 mg. She was given a diet high in protein; by November 3 there was no demonstrable edema, and by November 16 the blood creatinine had fallen to 2.9 mg. On November 13, there was again definite edema, without a change in the laboratory observations to account for it. The urine, throughout, showed from a trace to a large trace of albumin, a few casts and a few red cells. She was discharged on November 27, still slightly edematous. She died in June 1932.

CARDIOVASCULAR STATUS OF DIABETIC PATIENTS AFTER THE FOURTH DECADE OF LIFE

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An analysis of the cardiovascular status of the diabetic patient involves chiefly a study of the interrelationship of arteriosclerosis and diabetes. One hundred and twenty cases in patients above the age of 39 have been observed with this in view. The data presented here deal with the incidence of the important cardiovascular variants, and with their relation to age and sex and to the severity and duration of diabetes. To these are added some observations on the clinical types of arteriosclerosis in diabetic patients and on the significance of retinitis and abnormalities of the electrocardiogram. The primary data are tabulated in table 1 and summarized in table 2. The relation to sex is shown in table 3 and to age in table 4.

CARDIOVASCULAR VARIANTS

Cardiac Enlargement.—The heart in nondiabetic arteriosclerotic patients is as often small as large. In the autopsy material analyzed by Cabot,[1] 64 per cent of all patients (951) with arteriosclerosis [2] had large hearts; but excluding patients with pericarditis, valvular lesions, nephritis and some other unspecified lesions the incidence of cardiac hypertrophy was only 46 per cent, and excluding the first three groups only it was 39 per cent. The striking feature of these observations is the frequent absence of cardiac enlargement in patients with arteriosclerosis. Attention has heretofore been directed to the relation of arteriosclerosis to cardiac hypertrophy. The reverse of the picture is equally important. In general, it may be said that somewhat more than half of the patients with uncomplicated arteriosclerosis and somewhat less than half of those with complicated arteriosclerosis have small hearts at death, the percentage varying with the complicating factor and other determining influences, such as age at death and sex.

In this series of diabetic patients, which includes some with potential as well as those with manifest arteriosclerosis, the percentage of inci-

From the medical service and the outpatient department of the Sydenham Hospital.

1. Cabot, Richard C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, pp. 417 and 423.

2. These probably include some diabetic patients.

TABLE 1.—*Summary of Observations on 120 Cases of Diabetes Mellitus in Persons Aged Over 39*

1	2	3	4	5	6	7	8	9	10	11	12
Case	Age	Sex	Blood Pressure	Size of Heart	Aorta	Fundus	Electrocardiogram	Duration of Diabetes	Severity of Diabetes	Cardiac Symptoms	Complications
1	53	F	0 to +	+	..	++	(1931) T_3 flat; low voltage QRS (1933) T_3 inverted; premature auricular contractions; QRS normal; LAD	+++	++	None	Furunculosis; cholecystitis (?)
2	56	F	+	+	..	+	T_3 flat; T_3 inverted; LAD	++	+	Dyspnea; palpitation	None
3	72	M	+	+	++	..	T_1 diphasic; LAD	++	++	Dyspnea; slight decompensation	Transient loss of vision
4	51	M	0	0	..	..	T_3 flat; low voltage QRS	++	++	None	None
5	64	F	+ to 0	+	++	++	T_3 inverted	++	++	Dyspnea; palpitation	Bronchopneumonia
6	63	F	0	..	..	+	T_1 flat; $T_{3\ 3}$ inverted; LAD	+++	++	Slight dyspnea; palpitation	Cataract
7	46	F	0	0	0	0	T_3 flat; LAD	++++	+	Slight dyspnea	None
8	64	F	+ to 0	+	+++	+ to ++	Deep Q_3; LAD	+++	+	None.	Fever of unknown origin
9	45	M	0	0	+	0	T_1 flat; low voltage QRS; LAD; 5 records in six months	+	+	None	Osteomyelitis of foot
10	62	F	+	0	+++	+	(1930) T_3 flat; low voltage QRS; LAD (1932) T_3 flat; normal QRS; LAD (1933) T_1 flat; LAD	+++	++	Dyspnea; palpitation; edema of ankles	Cerebral thrombosis; hemiplegia
11	65	F	+	0	++	0	LAD	+++	+	None	Cholecystitis
12	62	M	0	0	++	+	T_3 inverted; LAD	+	+	None	Infection of finger
13	61	M	0	+	+++	..	Normal	++	+	None	Cholecystitis; syphilis
14	69	M	+	++	+++	..	Prolonged auriculoventricular conduction; LAD	+++	+	Dyspnea	None
15	85	M	+	++	++	++	LAD	..	+	Slight dyspnea on exertion	Cataracts
16	64	F	+ to 0	0	0	++	T_3 flat	++	+	None	None
17	52	F	+	+	+	+	T_3 inverted; LAD	++	+	Palpitation; dyspnea	None
18	58	F	+	++	+	..	T_{123} inverted; LAD	+	+	Substernal pain; dyspnea; palpitation; decompensation	None
19	75	F	+	++	+++	..	T_3 inverted; LAD	++	+	None	Carcinoma of bladder
20	46	M	0	..	..	0	T_3 inverted; LAD	+++	+	None	None
21	59	F	+	+	0	+++	(1929) T_1 inverted (1930) T_1 flat (1931) Normal	+++	++	None	Infection of upper respiratory tract
22	57	F	0 to +	..	..	+	T_3 inverted; LAD	+	+	None	None
23	76	M	0	..	..	++	Auricular fibrillation; intraventricular block; T_1 inverted; LAD	++	+	Precordial pain; dyspnea; decompensation	None
24	68	F	0	+	+++	+	(1931) T_3 inverted; LAD (1933) T_{23} inverted; LAD	++	+	Dyspnea on exertion	Carbuncle of scalp; purpura simplex

25	50	F	+	..	..	++	T_3 flat; T_3 inverted; LAD	+++	+++	None	None
26	42	F	0	0	0	0	T_3 inverted; low voltage QRS; LAD	++	+	None	None
27	58	F	0	+	+	0	T_3 inverted; premature auricular and nodal contractions; LAD	++	+++	Precordial pain; palpitation	None
28	48	F	0	0	..	+	(1933) T_{123} flat; LAD (1933) T_3 inverted; LAD	+	+	None	None
29	49	F	+	+	++	..	T_3 inverted; LAD	+++	++	Precordial pain	None
30	60	F	+	+	+	+	T_3 inverted; LAD	+++	+	Palpitation; slight decompensation	Psoriasis
31	68	F	+ to 0 to +	0	+++	+++	(1929) LAD (1930) LAD (1932) T_1 diphasic; LAD	+++	++	None	Partial loss of vision
32	69	M	+	+++	+++	++	T_1 inverted; T_3 flat; LAD	+	+	Dyspnea; palpitation on exertion	Cerebral arteriosclerosis; senile psychosis
33	53	F	0	0	+++	0	LAD	+++	+	None	None
34	60	F	0 to +	..	..	+++	T_3 inverted; deep Q_3; LAD	+++	++	None	Infection of foot
35	48	F	0	..	..	+	T_3 flat	+++	+++	None	None
36	69	M	0	0	+++	0	(1927, 1930 and 1932) T_3 flat; LAD	+++	++	None	Infection of hand and buttock
37	49	F	+ to 0	+	+	0	T_3 flat; LAD	+++	+	Dyspnea on exertion	Hallux valgus
38	43	F	+	+	0	++	T_3 inverted; LAD	+++	+	None	None
39	49	F	+	0	++	0	T_3 inverted; LAD	++	++	None	None
40	42	M	0	0	0	..	T_3 flat; low voltage QRS; LAD	++++	+	None	None
41	45	F	+ to 0	++	..	+	T_3 inverted; LAD	++++	+++	None	None
42	44	F	0	0	0	0	Low voltage QRS	++++	+	Palpitation	None

* Column 2: Age is recorded as of the last observation.

Column 4: 0 indicates a blood pressure up to 150 mm. of mercury systolic or 100 mm. diastolic; + a pressure of over 150 mm. systolic or 100 mm. diastolic.

Column 5: 0 indicates a normal or small heart; +, a slight or questionable enlargement; ++, a moderate enlargement, and +++, a more than moderate enlargement. The size of the heart was determined in most cases by fluoroscopic examination and in some cases by teleroentgenograms. Enlargement of the left ventricle posteriorly, if not associated with notable enlargement to the left, was graded +. Measurements of teleroentgenograms were made but were used only in confirmation of general appearance and contour.

Column 6: 0 indicates a normal aorta; +, increased density; ++, dilatation, increased density and calcification, and +++, dilatation, increased density and calcification of a greater degree with elongation and coiling.

Column 7: 0 indicates a normal fundus; +, thin arteries or spasm; ++, thin arteries, spasm and retinal degeneration, and +++, thin arteries, spasm and hemorrhages.

Column 8: Not graded in this table. All significant or probably significant abnormalities of the electrocardiogram are included. LAD indicates left axis deviation.

Column 9: Duration of diabetes is recorded as of the last observation: + indicates a duration of less than one year; ++, of from one to four years; +++, of from four to nine years, and ++++, of ten years or over.

Column 10: Severity of diabetes is graded +, ++ and +++. The grading is based in each case on comparatively loosely applied criteria. These were: (1) the ease or difficulty with which control was established and maintained; (2) the level of carbohydrate tolerance, and (3) the frequency of infection. Control was indicated by sugar-free urine and a blood sugar before breakfast of below 200 mg. per 100 cc. on a fixed dietary and insulin regimen. In general, if the urine remained sugar-free in all specimens on diets of 100 Gm. of carbohydrate or over with maintenance of caloric intake, no attempts were made to reduce the blood sugar, unless it exceeded 200 mg. per 100 cc. The criteria of carbohydrate tolerance with metabolic control were: +, indicates 100 Gm. or higher of carbohydrate without insulin and with moderate blood-sugar levels; ++, less than 100 Gm. of carbohydrate without insulin or 100 Gm. of carbohydrate with less than 25 units of insulin daily; +++, higher insulin requirements, irregular insulin distribution or irregular blood sugar curves. The estimates fom the tolerance level were modified by the factors of the ease of control and the appearance of complicating infections. Only grade + cases were considered mild.

Columns 11 and 12: Cardiac symptoms and complications include only those during the period of observation, or immediately preceding it. The period of observation for my cases varied from less than one month to five years and for those of others, up to ten years.

TABLE 1.—*Summary of Observations on 120 Cases of Diabetes Mellitus in Persons Aged Over 39 *—Continued*

1	2	3	4	5	6	7	8	9	10	11	12
Case	Age	Sex	Blood Pressure	Size of Heart	Aorta	Fundus	Electrocardiogram	Duration of Diabetes	Severity of Diabetes	Cardiac Symptoms	Complications
43	41	F	0 to + to 0	0	++	..	Normal	+++	+	None	Cholecystitis; xanthoma
44	51	F	+	++	..	+++	(1931) T_{12} inverted (1932) T_{12} inverted deeply	++++	+	Substernal pressure; dyspnea; edema; decompensation; death	None
45	44	M	0	0	+++	0	Low voltage QRS	+	++	None	None
46	54	F	+	0	+++	..	T_{123} diphasic (digitalis)	++	+	Dyspnea; palpitation	None
47	58	F	+	0	+++	..	T_3 flat; low voltage QRS; LAD	+++	++	None	Pulmonary tuberculosis
48	51	F	0	0	..	+++	.....	++	++	Dyspnea on exertion	None
49	65	F	0	0	++	+	LAD	..	++	None	None
50	48	M	0	0	0	..	LAD	+++	++	Dyspnea	Chronic bronchitis; bronchiectasis
51	62	M	0	0	..	..	Peaked T wave	++++	+	None	Infection of arm
52	60	F	0 to +	0	0	0	T_{12} inverted; low voltage QRS; LAD	+++	++	Substernal compression; dyspnea	Asthma
53	54	F	0 to +	+	0	0	T_3 flat; LAD	+	+	None	Fracture of toe
54	46	F	+	0	..	0	LAD	+	+++	Palpitation	Healed mitral stenosis
55	49	F	+ to 0	+	..	+	Slurred QRS; LAD	+	+	None	None
56	50	F	0	++	+++	+	.....	+	..	None	Infection of foot
57	60	F	+ to 0 to +	0	0	0	(1930) LAD (1931) Transient auricular fibrillation; LAD	++	++	None	Appendicitis
58	41	F	+	0	0	+	T_3 inverted; LAD	++++	+++	Substernal compression; dyspnea; palpitation	None
59	40	M	0	0	+	0	.....	++	++	None	None
60	50	F	0	0	+	+	T_3 flat; LAD	++	+	None	Syphilis
61	59	F	0	..	..	+	Intraventricular block; wide, low voltage QRS; T waves upright	++++	+	Palpitation; precordial and substernal pain	Cerebral concussion; fractures of clavicle and three ribs
62	49	F	+	+	+++	0	Normal	+++	+	None	None
63	52	F	+	..	..	+	T_2 flat; T_3 inverted; LAD	++	++	Precordial pain; dyspnea	Furunculosis
64	65	F	+ to 0	+	..	+++ to ++	LAD	++++	+	None	Psoriasis; cataract
65	64	M	0	0	0	0	T_2 flat; T_3 inverted	++	+++	None	Active pulmonary tuberculosis
66	64	F	+	0	+++	+	Normal	++	+	None	None
67	64	F	0	..	..	++	T_3 inverted; LAD	++++	++	Dyspnea	Pyelonephritis; uremia (fatal)
68	42	F	+ to 0	+	..	+	T_3 inverted	++	+	Dyspnea	Menorrhagia; ulcer of leg
69	59	F	0	0	0	0	(1928, 1930 and 1932) T_3 flat	++++	++	None	None
70	72	F	+	+++	+++	+	(1930 and 1931) T_3 inverted; LAD	++	+	Dyspnea; substernal pain	None

71	66	M	..	0	++	+	Normal	+++	+	Dyspnea	None
72	51	F	0	0	..	++	T_{123} flat; low voltage QRS	++	++	None	Hysteria
73	53	F	0 to +	..	..	+	T_3 inverted; LAD	++	+	Dyspnea	Rheumatoid arthritis
74	49	M	0	..	..	+	T_3 inverted; LAD	++	+	None	Inguinal hernia (herniotomy)
75	58	F	0	..	..	+++	Deep Q_3; LAD	++	++	None	Infection of toe
76	69	F	+	++	+++	+++	(June 1929) LAD (Dec. 1929) T_1 inverted; LAD (1932) T_{12} inverted; LAD	++++	+	Dyspnea; precordial pain; decompensation	Hallux valgus; infection of foot; cerebral thrombosis; hemiplegia
77	64	F	0	+	+++	..	T_{23} inverted	+	++	Dyspnea	Cataracts
78	48	F	+	0	..	0	T_3 inverted; LAD	+	+	None	Glaucoma
79	74	F	+	..	..	++	T_1 inverted; T_3 flat; low voltage QRS; LAD	++	++	Dyspnea	None
80	65	F	+	0	..	+	(1932 and 1933) T_{123} flat	++	+	Dyspnea; substernal pain	Cataract
81	55	F	+	+++	+++	++	T_1 inverted; LAD	++	+	Dyspnea; palpitation	Syphilis
82	62	F	+ to 0	..	..	+++ to +	Normal	++++	++	None	Prolapse of uterus; cataracts
83	64	M	0	0	+++	0	(1927) T_3 inverted; LAD (1928) T_{123} flat; LAD (1932) T_{123} flat; low voltage QRS; LAD	+++	+	Dyspnea	Prostatic hypertrophy
84	60	M	0	0	+++	0	T_3 flat; LAD	++++	+	None	None
85	63	F	+	0	+++	+	Normal	++++	+	Edema of legs	None
86	57	F	0	++	++	+	T_3 inverted; LAD	++++	+	None	None
87	70	F	+ to 0 to +	+	+++	..	(1925) LAD (1926 and 1928) T_3 inverted; LAD (1930) T_{12} diphasic; LAD; (diabetes discovered) (1932) T_1 flat; T_{23} inverted; LAD	++	++	Substernal pain; dyspnea	Cataracts
88	41	M	0	0	0	0	Normal	++	+++	None	Pulmonary tuberculosis
89	44	F	+	++	0	0	Intraventricular block; T_2 diphasic; T_3 inverted; LAD	+	+	None	None
90	60	F	+	+	+++	0	T_{12} inverted; LAD	++++	++	None	None
91	47	F	0 to +	0	++	0	T_3 flat	+++	++	Palpitation	Infection of the upper respiratory tract
92	58	F	0	++	+++	+	T_{123} inverted; wide QRS; LAD	+	+	Precordial pain; dyspnea	None
93	62	M	0	..	..	+	T_3 flat; LAD	++++	++	None	Prostatectomy; carbuncle; osteomyelitis of humerus
94	55	F	0	..	..	++	(1929) T_3 inverted; LAD (1932) T_{12} inverted; wide QRS; LAD	++++	+	Substernal pain; dyspnea; palpitation	Carbuncle of neck
95	48	F	+	+	++	+	T_3 inverted; ventricular premature contractions	+++	+	Dyspnea	Carbuncle of back; rheumatoid arthritis; sensitivity to insulin (urticaria)
96	50	F	+ to 0	++	+++	++	T_3 inverted; LAD	+++	++	Dyspnea	Cholecystitis
97	48	F	+	..	..	+ to +++	(1928) T_{12} diphasic; T_3 inverted; LAD (1932) T_1 diphasic; LAD	++++	++	Precordial pain; dyspnea	None

TABLE 1.—*Summary of Observations on 120 Cases of Diabetes Mellitus in Persons Aged Over 39 *—Continued*

1	2	3	4	5	6	7	8	9	10	11	12
Case	Age	Sex	Blood Pressure	Size of Heart	Aorta	Fundus	Electrocardiogram	Duration of Diabetes	Severity of Diabetes	Cardiac Symptoms	Complications
98	45	F	0	0	0	0	T_3 variable	+++	++	None	Cholecystitis; hysteria
99	70	M	+	0	..	+	LAD	+	+	None	Intermittent claudication
100	53	F	+	+	+++	+	T_3 Inverted; LAD	+	+	Dyspnea	None
101	60	F	0	0	0	0	(1929) LAD (1932) T_3 inverted; LAD	++++	+	None	Hysteria
102	60	M	0	0	0	0	T_3 flat; LAD	+++	++	None	None
103	72	F	+	0	+++	+	T_1 diphasic; low voltage QRS	+++	+	None	Cataracts
104	67	F	+	0	+++	+	(1924) Deep Q_3; LAD (1930) T_{123} inverted; wide QRS; LAD	+++	++	Dyspnea; palpitation; decompensation (terminal)	None
105	52	F	0	..	..	+	T_3 inverted; LAD	++	++	Dyspnea; palpitation precordial pain	None
106	62	F	+	0	..	+	LAD	++++	+	None	None
107	53	F	0	0	+++	+	T_1 diphasic; low voltage QRS	+++	+	None	Coma; rheumatoid arthritis
108	42	F	0	0	+	..	Normal	++++	++	Dyspnea; palpitation; precordial pain	Cervical lymphadenitis
109	56	F	0	+	++	0	(1929 and 1933) T_3 flat; LAD	+++	+	None	Fistula in ano; furunculosis; chronic cystic mastitis
110	58	F	+	0	++	+	LAD	+++	+	None	Arthritis
111	69	F	+	++	+++	..	Intraventricular block; delayed auriculoventricular conduction; T_{123} inverted	++	+	None	Kerato-iritis (traumatic); cataracts
112	40	M	0	0	..	+++	(1931) T_3 inverted (1932) T_3 diphasic; T_3 inverted	+++	+	None	Pulmonary tuberculosis
113	47	M	0	+	+	..	T_3 flat	+	++	None	None
114	68	F	+	0	+++	+	T_3 inverted; LAD	+++	+	Precordial pain; dyspnea; palpitation	None
115	44	F	0	+	+	+++ to +	T_3 inverted; LAD	++	++	None	Pyelitis; fibroid uterus; furunculosis
116	64	F	+ to 0 to +	+	0	+ to +++ to +	(1929-1930) Normal (1931) T_1 diphasic; LAD (1932) T_1 flat; LAD (1933) T_1 diphasic; LAD	+++	+	Substernal pain; palpitation; decompensation	Fracture of wrist
117	41	F	0 to +	+	+	+	(1930) T_1 inverted; LAD (1931-1932-1933) T_1 diphasic; wide QRS; LAD	++	+	Dyspnea; palpitation; precordial pain	Nephrolithiasis; cholecystitis; fibroid uterus
118	42	F	0	0	0	..	T_3 inverted; deep Q_3; LAD	++	+	None	None
119	61	F	+	++	+++	+	T_1 inverted; LAD	+++	++	Substernal pain; dyspnea; palpitation	Cerebral thrombosis (fatal)
120	47	F	+	++	++	+	(Mar. 1931) T_3 inverted; LAD (Nov. 1931) T_2 diphasic; T_3 inverted; LAD (1932) T_1 flat; T_{23} inverted	++	+	Precordial pain	None

dence of cardiac enlargement was similar to that in Cabot's series, composed entirely of patients with manifest arteriosclerosis. Slightly more than one half (53 per cent) had small or normal-sized hearts, and slightly less than one half (47 per cent) had enlarged hearts; but in only 18 per cent was the enlargement more than slight. Cardiac enlargement was not much more frequent in these diabetic patients than in those with otherwise uncomplicated arteriosclerosis, and considerably less frequent than in those with otherwise complicated arteriosclerosis. In less than one fifth of diabetic patients past the fourth decade of life is there any considerable hypertrophy.

Cardiac enlargement in diabetes is twice as frequent in females as in males (table 3) if a slight degree of enlargement is included, and only slightly more frequent if the grade 1 type of enlargement is excluded.

TABLE 2.—*Percentage Incidence of Cardiovascular Abnormalities*

	Incidence	Total Cases Analyzed
Atherosclerosis of aorta (grades 1, 2 and 3)	75%	83
Atherosclerosis of aorta (grades 2 and 3)	60%	83
Retinal arteriosclerosis	69%	101
Retinitis	28%	101
Hypertension (transient and permanent)	50%	119
Hypertension (permanent)	38%	119
Enlarged heart (grades 1, 2 and 3) (including slight enlargement)	47%	101
Enlarged heart (grades 2 and 3) (excluding slight enlargement)	18%	101
Abnormalities of electrocardiogram (abnormalities of T_1 or T_2 and conduction defects)	35%	117
Abnormalities of electrocardiogram (including also low voltage QRS and deep Q_3)	45%	117
Left axis deviation	73%	117
Cardiac symptoms (including slight and variable symptoms and pain of all types)	46%	120
Cardiac decompensation (including two cases with angina pectoris)	8%	120
Cardiac pain	19%	120
Angina pectoris	9%	120

In the fifth decade of life, cardiac enlargement is less frequent than the average for all ages together. The percentage rises in the sixth decade and then drops sharply in the seventh and later decades. A perusal of table 4 will show that the precipitate fall in the incidence of cardiac enlargement after the sixth decade is in sharp contrast to the steady increase with age in the incidence of most cardiovascular abnormalities. It may be attributed to one or more of three possible factors: (1) the effect of a debilitating disease, (2) premature death of patients with enlarged hearts in the sixth decade of life and (3) the appearance of new cases of diabetes without cardiac enlargement at advanced ages (Allbutt's decrescent arteriosclerosis). Of these three factors, the first may be considered of negligible importance under the present conditions of metabolic control; the second seems to me to be of less importance than the third; the last two together adequately explain this unusual decrease.

The results of the autopsy studies of Nathanson [3] agree with these clinical observations. In 98 cases 86 per cent of which were in patients beyond the fourth decade of life, the heart was enlarged to more than 450 Gm. in 17 per cent. Including enlargements over 400 Gm., the incidence of cardiac hypertrophy was 41 per cent. The close agreement with the percentages shown in table 2 is partly accidental, since the distributions according to age and sex in his series are different than in this. Warren [4] reported that only 31 per cent of 283 diabetic patients showed enlargement of the heart to above 350 Gm., but his cases included those of all ages.

TABLE 3.—*Percentage Incidence of Cardiovascular Abnormalities by Sex*

	Male	Female
Retinal arteriosclerosis	47%	74%
Retinitis	21%	29%
Hypertension (transient and permanent)	19%	67%
Hypertension (permanent)	19%	43%
Atherosclerosis of aorta (grades 2 and 3)	58%	61%
Enlarged heart (grades 1, 2 and 3)	26%	53%
Enlarged heart (grades 2 and 3)	13%	19%
Abnormalities of electrocardiogram (abnormalities of T_1 or T_2 and conduction defects)	31%	36%

TABLE 4.—*Percentage Incidence of Cardiovascular Abnormalities by Age*

	40 to 49 Years	50 to 59 Years	60 Years and Over
Retinal arteriosclerosis	47%	82%	77%
Retinitis	13%	34%	33%
Hypertension (transient and permanent)	46%	51%	67%
Hypertension (permanent)	30%	36%	45%
Atherosclerosis of aorta (grades 2 and 3)	31%	63%	79%
Enlarged heart (grades 1, 2 and 3)	39%	60%	44%
Enlarged heart (grades 2 and 3)	9%	28%	19%
Abnormal electrocardiogram (abnormalities of T_1 or T_2 and conduction defects)	19%	39%	44%

The clinical and autopsy data, disregarding the differences arising from sex and age distribution, are adequate to prove the relative infrequence of cardiac enlargement in diabetic cases in the arteriosclerotic zone. The published data from autopsies are not sufficient to confirm the sex and age differences which are indicated in tables 3 and 4.

Hypertension.—Major [5] has shown that at comparably advanced ages, the frequency of hypertension above 150 mm. of mercury is higher in diabetic patients than in otherwise normal controls, or than

3. Nathanson, M. H.: Coronary Disease in One Hundred Autopsied Diabetics, Am. J. M. Sc. **183**:495, 1932.

4. Warren, S.: The Pathology of Diabetes, Philadelphia, Lea & Febiger, 1930, p. 148.

5. Major, S. G.: Blood Pressure in Diabetes Mellitus, Arch. Int. Med. **44**:797 (Dec.) 1929.

in the general hospital or clinic population. His percentages and also Kramer's [6] were somewhat lower than those shown in table 4. Both these, as well as other, investigators have demonstrated the increasing incidence of hypertension with advancing age. In the present series the rise was uninterrupted from 46 per cent in the fifth decade to 67 per cent in the seventh and later decades, but the series included many cases of transient hypertension. Excluding the latter, the incidence increased from 30 per cent in the fifth to 45 per cent in the seventh and later decades, which conforms more closely to that in Major's larger series and also to Sherril's [7] results.

Permanent hypertension in association with diabetes is over twice as frequent among females as among males. Including transient hypertension, it is three and one-half times as frequent.

Arteriosclerosis of the Aorta and Retinal Arteries.—Arteriosclerosis in either the aorta or the retinal arteries was present in 89 per cent of these patients; in both the aorta and the retinal arteries, in 51 per cent. The high incidence of vascular disease in diabetic patients past the fourth decade, now widely recognized, is indicated in table 2. It occurred in the aorta in 75 per cent of the patients, with dilatation in 60 per cent. It was present in the retina in 69 per cent. Involvement of each of these organs showed a greater incidence in females than in males, but the differences are less marked in the case of aortic arteriosclerosis. As might be expected, the percentages increase with age, the sharpest increase being between the fifth and the sixth decade. In the case of aortic arteriosclerosis, the increase continues into the seventh decade; for retinal arteriosclerosis, it diminishes slightly.

Retinitis.—The retinitis of diabetes is the arteriosclerotic retinitis first described as such by Moore [8] and distinguished by him from the retinitis of nephritis. Some [9] still dispute this view, chiefly because of the failure to distinguish arteriosclerotic nephritides from the other types. In the diabetes of childhood and adolescence, retinitis is rare,[10] and when found it is usually in the very severe or badly controlled cases. The incidence increases with age from a relatively low value (13 per cent) in the fifth decade (table 3) to 34 per cent in the sixth. Follow-

6. Kramer, D. W.: Hypertension and Diabetes, Am. J. M. Sc. **176**:23, 1928.

7. Sherril, J. W.: Cardiovascular Disease in Diabetes Mellitus, California & West. Med. **38**:73; **39**:17, 1933.

8. Moore, R. F.: The Retinitis of Arteriosclerosis and Its Relation to Renal Retinitis and to Cerebral Vascular Disease, Quart. J. Med. **10**:29, 1917.

9. Bessière, E.: Existe-t-il une rétinite diabétique en l'absence d'altérations rénales? Arch. d'ophth. **49**:219, 1932.

10. White, Priscilla: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, pp. 193 and 217. Wagener, H. P., and Wilder, R. M.: The Retinitis of Diabetes Mellitus, J. A. M. A. **76**:515 (Feb. 19) 1921.

ing this, there is no further increase. Females were found to have retinitis only slightly more frequently than males. Every patient with retinitis had also retinal arteriosclerosis, inevitably, in view of its arteriosclerotic origin. Spalding and Curtis [11] found a similar association. The total incidence of retinitis in their patients was lower than that (28 per cent) found in this series, but they included persons below the age of 40. It should be noted that after the fourth decade retinitis develops in 4 of every 10 patients with retinal arteriosclerosis.

Abnormalities of the Electrocardiogram.—Abnormalities of the T waves in leads I and II occurred in 39 out of 117 patients, an incidence of 33 per cent. Of these, 9 also had a low voltage QRS complex; 3 had intraventricular block, 1 with delayed auriculoventricular conduction time and another with auricular fibrillation; 4 had a widened QRS complex, and 1 of these, a deep Q_3 wave. Of the 78 patients without abnormalities of the T wave, 1 had delayed auriculoventricular conduction time; 1, intraventricular block; 1, transient auricular fibrillation; 7, a low voltage QRS complex, and 4, a deep Q_3 wave. There were no patients with right axis deviation. Left axis deviation was present in 85 patients (73 per cent). Of the patients with otherwise normal T waves, 51 (65 per cent) had a flattened or inverted T_3 wave.

If one includes as significant only abnormalities of the T wave in leads I and II and defects in conduction (excluding transient auricular fibrillation), there were 41 (35 per cent) grossly abnormal records. Including all the abnormalities mentioned there were 53 (45 per cent). Hepburn and Graham [12] found an incidence of 45.5 per cent, including, however, patients of all ages and with minor electrocardiographic abnormalities. They also demonstrated the increased incidence with advancing age which is shown in table 4. The sharpest increase here was between the fifth and the sixth decade. The percentage of incidence was also slightly higher in females than in males (table 3).

Cardiac Symptoms, Cardiovascular Sequelae and Complications.—Cardiac symptoms were absent in 65 patients (54 per cent). There were 10 patients (8 per cent) with cardiac decompensation, of whom 2 died; 23 patients (19 per cent) had cardiac pain, but of these only 11 (9 per cent) were considered to have angina pectoris. One of the latter died as a result of cerebrovascular insult. Most of the others with cardiac symptoms had slight evidence of impairment of cardiac reserve. Besides the patient who died there were 2 (2.5 per cent) who had cere-

11. Spalding, E. M., and Curtis, W. S.: Retinitis and Other Changes in the Eyes of Diabetics, Boston M. & S. J. **197**:165, 1927.

12. Hepburn, J., and Graham, D.: An Electrocardiographic Study on One Hundred and Twenty-Three Cases of Diabetes Mellitus, Tr. A. Am. Physicians **43**:86, 1928.

bral thrombosis and hemiplegia and 1 with senile psychosis and cerebral endarteritis. There was 1 patient with intermittent claudication, but in no instance did gangrene of the lower extremities appear. As in the experience of others, the most frequent complication was infection (abscesses, furuncles and osteomyelitis), which occurred in 16 cases (13.3 per cent). In 5 cases there was infection of the feet. Other complications were cholecystitis (9 cases), pulmonary tuberculosis (4), cataract (8), arthritis (4), syphilis (3) and pyelonephritis (2). Miscellaneous complications included glaucoma, psoriasis, xanthoma, fractures and hysteria.

RELATION OF FACTORS TO DIABETES

Age and Sex Distribution.—Patients above the age of 39 now represent roughly about nine tenths of the total diabetic population.[13] Before the era of insulin the percentage of patients with diabetes past the fourth decade was already rising,[14] owing to the combined factors of the aging of the general population and the preponderant incidence of diabetes with late onset (two thirds of all the cases begin after the age of 39, and three fourths of those of ten years' duration).[15] The diabetic population may now be said to be aging for these reasons as well as because of the demonstrable lengthening of the life span of diabetic patients in the Banting era, in which an increasing number are brought into the later decades of life.[16] This series represents, therefore, a small cross-section of a large part of the typical diabetic population, considered from the standpoint of age distribution. By decades the distribution is as follows: in the fifth, 37 patients; in the sixth, 33; in the seventh, 41, and in the eighth and later ones, 9.

The sex distribution in these cases is somewhat atypical. There were 27 males and 93 females (77.5 per cent); that is, the distribution is heavily weighted for females. In other series of diabetic cases, the excess of females has generally been much smaller, and in some the number of cases has been about equally divided between males and

13. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: Its Incidence and the Factors Underlying Its Variations, Am. J. M. Sc. **187**:433, 1934.

14. Emerson, H., and Larimore, L. D.: Diabetes Mellitus: A Contribution to Its Epidemiology Based Chiefly on Mortality Statistics, Arch. Int. Med. **34**:585 (Nov.) 1924.

15. (*a*) Joslin, E. P.: Diabetes: Its Control by the Individual and the State, Boston, Harvard University Press, 1931, p. 46; (*b*) The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 675; (*c*) The Ten-Year Diabetic, Am. J. M. Sc. **175**:472, 1928.

16. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: Characteristics and Trends of Diabetes Mortality Throughout the World, Am. J. M. Sc. **186**:753, 1933.

females, as in John's [17] first series of 1,000 cases. In New York City, however, deaths from diabetes, as recorded in death certificates, showed the unusual sex distribution noted in my series.[18] Among 1,784 patients dying of diabetes in 1930 there was an equal proportion of males and of females up to the age of 35. After this age the percentage of females increased, until at 55 and over the ratio of females to males was 2:1. Joslin, Dublin and Marks [16] recently found a similar distribution in the mortality of holders of industrial life insurance policies. In Wendt and Peck's [19] analysis, the ratio of females to males was 3:1 in the sixth decade, and more than 2:1 in the fifth. A high incidence of females among patients with diabetes past the fourth decade probably represents an accurate estimate of the typical sex distribution.

Relation of Cardiovascular Abnormalities to Age and Sex.—All the cardiovascular variants studied show a higher incidence in females than in males (table 3). The least variation by sex was in the case of atherosclerosis of the aorta, the greatest for transient hypertension. The differences for retinitis and electrocardiographic abnormalities were slight in comparison with those for hypertension and cardiac enlargement. Kramer [6] found a similar sex linking for hypertension among his diabetic patients.

The incidence of each cardiovascular variant is higher in the sixth decade than in the fifth. After the sixth decade atherosclerosis of the aorta, hypertension and abnormalities of the electrocardiogram continue to increase in frequency. The incidence of the other abnormalities diminishes slightly, but the frequency of enlargement of the heart drops sharply. The reasons for this have already been discussed. The increasing incidence of most cardiovascular abnormalities in persons with diabetes with advancing age has been generally recognized;[20] it parallels similar increases among nondiabetic persons. Only in respect to hypertension,[5] and less satisfactorily in respect to calcification of the peripheral arteries,[21] have direct comparisons at comparable ages

17. John, H. J.: Diabetes: A Statistical Study of One Thousand Cases, Arch. Int. Med. **39**:67 (Jan.) 1927.

18. Week. Bull., New York City Health Dept. **20**:357, 1931.

19. Wendt, L. F. C., and Peck, F. B.: Diabetes Mellitus: A Review of 1,073 Cases, 1919-1929, Am. J. M. Sc. **181**:52, 1931.

20. Morrison, L. B., and Bogan, I. K.: Calcifications of the Vessels in Diabetes, J. A. M. A. **92**:1424 (April 27) 1929. Gray, P. A., and Sansum, W. D.: The Higher Carbohydrate Diet Method in Diabetes Mellitus, ibid. **100**:1580 (May 20) 1933. Leutenegger, F.: Diabetes Mellitus und Gefässystem, Ztschr. f. klin. Med. **119**:164, 1931.

21. Bowen, B. D., and Koenig, E. C.: Arteriosclerosis and Diabetes Including a Roentgenological Study of the Lower Extremities, Bull. Buffalo Gen. Hosp. **5**:31, 1927.

been made to determine the relative frequency in diabetic and nondiabetic persons. These indicate a higher frequency in persons with diabetes.

Relation of Cardiovascular Abnormalities to the Severity and Duration of Diabetes.—Because of the lack of directly comparable data on the relative incidence of cardiovascular abnormalities in diabetic and

TABLE 5.—*Percentage Incidence of Cardiovascular Abnormalities by Age and Severity of Diabetes*

	Retinal Arterio-sclerosis		Retinitis		Aortic Athero-sclerosis, Grades 2 and 3		Hyper-tension		Enlarged Heart, Grades 1, 2 and 3		Abnormal Electro-cardiogram T_{12} and Conduction Defects	
	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
40 to 49 years.....	50%	42%	11%	17%	29%	33%	52%	44%	45%	29%	29%	7%
50 to 59 years.....	82%	82%	18%	64%	69%	40%	58%	42%	71%	44%	42%	36%
60 years and over...	82%	67%	33%	33%	83%	75%	70%	65%	46%	40%	38%	62%
Total.....	73%	68%	22%	37%	64%	53%	62%	52%	51%	37%	36%	38%
Number of cases....	100		100		82		118		100		117	

TABLE 6.—*Percentage Incidence of Cardiovascular Abnormalities by Age and Duration of Diabetes*

	Retinal Arterio-sclerosis		Retinitis		Aortic Athero-sclerosis, Grades 2 and 3		Hyper-tension		Enlarged Heart, Grades 1, 2 and 3		Abnormal Electro-cardiogram T_{12} and Conduction Defects	
	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over
40 to 49 years.....	44%	50%	6%	22%	25%	36%	44%	53%	41%	38%	29%	11%
50 to 59 years.....	88%	77%	25%	46%	50%	78%	53%	50%	64%	55%	35%	43%
60 years and over...	85%	70%	38%	30%	80%	76%	68%	68%	59%	33%	50%	43%
Total.....	71%	67%	22%	31%	54%	64%	53%	59%	54%	39%	39%	33%
Number of cases....	99		99		81		117		99		115	

nondiabetic persons, it is necessary to attack the problem of the effect of diabetes on the cardiovascular system by indirection. This has been attempted here by the correlation of each variant with the severity and duration of diabetes. The results are shown in tables 5 and 6.

The criteria used in separating the mild from the severe cases are given in the footnotes to table 1. They are in part arbitrary and open to criticism on several grounds. Rabinowitch,[22] for instance, suggested

22. Rabinowitch, I. M.: The Cholesterol Content of Blood Plasma in Diabetes Mellitus, Arch. Int. Med. **43**:363 (March) 1929.

the blood cholesterol level as a more reliable index of severity. This would seem important, particularly as it applies to the effect on the arterial system, but Shepardson [23] observed no notable differences in blood cholesterol in young diabetic patients with and without roentgenographic evidence of peripheral arteriosclerosis.

Retinitis is more frequent in severe than in mild cases of diabetes. In the sixth decade it is three and one-half times as frequent. Despite the fact that the retinitis of the diabetic patient is essentially an arteriosclerotic retinitis increasing in frequency with age, it is also directly influenced by the disturbance of carbohydrate metabolism. Only after the sixth decade is the incidence as high in the mild as in the severe cases.

With the one further exception of an abnormal electrocardiogram after the sixth decade, every other cardiovascular variant is more frequent, in the mild as in the severe cases, or at least as frequent. This seems to confirm the suggestion of some investigators [24] that diabetes has little if any effect on the severity of arteriosclerosis. Joslin, however, has offered abundant proof to the contrary, some of it hypothetical, but most of it factual and based on clinical and pathologic grounds, as well as on statistics of contributory causes of death.[25] It is to be noted that table 5 does not indicate that severe diabetes has no effect on the incidence of cardiovascular abnormalities. It seems to indicate that mild diabetes has a more pronounced effect than severe diabetes. This is a clue worth pursuing because it leads to another approach which is more in conformity with Joslin's views.

The diabetic population is not stationary. In each succeeding decade of life in the general population there are new diabetic recruits. At advanced ages the patients with recently acquired diabetes are not arteriosclerosis-free; in fact, they may have severe cases of arteriosclerosis, and it is well known that in these patients the disturbance of carbohydrate metabolism may be only slight. It is therefore not surprising to notice a close association between mild diabetes and the higher percentages of incidence of cardiovascular abnormalities.

If this explanation is correct, a high incidence of cardiovascular abnormalities should be found in cases of diabetes of recent origin in persons of advanced ages. This is demonstrated in table 6. With exceptions at some ages (but chiefly before the sixth decade), the incidence is higher in cases with a duration of less than five years than in those of five years' standing and over. The significance of these

23. Shepardson, H. C.: Arteriosclerosis in the Young Diabetic Patient, Arch. Int. Med. **45**:674 (May) 1930.

24. Nathanson,[3] Enklewitz, M.: Diabetes and Coronary Thrombosis, Am. Heart J. **9**:386, 1934.

25. Joslin,[15b] pp. 375 and 678.

facts is that elderly persons with severe arteriosclerosis in whom diabetes develops have cardiovascular abnormalities more frequently than persons in whom diabetes began earlier. The probable effect of diabetes on the initiation or intensification of arteriosclerosis is concealed in the tables by the accretion of new diabetic patients, already severely arteriosclerotic. These facts do not contradict the views of Joslin's school; neither do they, except indirectly, confirm them.

TYPES OF CARDIOVASCULAR DISEASE IN DIABETIC PATIENTS

Rheumatic and Syphilitic Cardiovascular Disease.—Rheumatic fever does not concern the diabetic patient, if only because of the wide divergence in the ages of onset. The cardiac sequelae of rheumatic fever are found in only a very small percentage of cases of diabetes. Concerning the arterial sequelae, there is as yet almost complete ignorance as concerns the nondiabetic and, perforce, the diabetic patient. In the absence of active infection rheumatic fever may be relegated to a place of minor importance, as to the manner in which it affects both the heart and the blood vessels of diabetic patients. Barach [26] found a history of rheumatic fever as frequent for his diabetic as for his nondiabetic patients, but the cardiac sequelae were much less frequent in the former group. He attributed this to a hereditary constitutional immunity of the potential diabetic patient to the cardiac lesions of rheumatic fever, a view of considerable interest in the light of the theories which link diabetes to the pituitary gland and the autonomic centers in the diencephalon.[27] In this series, there was but 1 instance of rheumatic endocarditis, and this was an inactive, healed lesion. The slightly higher incidence of other forms of arthritis in diabetes has no known bearing on the cardiovascular system.

Syphilis also is relatively uncommon in cases of diabetes. In this series there were 3 patients (2.5 per cent) with positive Wassermann reactions. Joslin [28] noted syphilis in 1.9 per cent of his cases; John,[29] in 2.7 per cent, although he cites higher per cents found by some other investigators. Accordingly, syphilitic aortitis, aneurysm and aortic insufficiency may be disregarded as infrequent in coincidence with diabetes. The possibility of a higher incidence of syphilitic myocarditis

26. Barach, J. H.: The Incidence of Rheumatic Heart Disease Among Diabetic Patients, Am. Heart J. **2**:196, 1926.

27. Penfield, W.: The Influence of the Diencephalon and Hypophysis upon General Autonomic Functions, Bull. New York Acad. Med. **9**:613, 1933.

28. Joslin,[15b] p. 754.

29. John, H. J.: Diabetes: A Statistical Study of Two Thousand Cases, Arch. Int. Med. **42**:217 (Aug.) 1928.

in the absence of positive serologic reactions, formerly a widely accepted theory, has fallen into disrepute, so that even Warthin [30] shifted his attention from the myocardium to the coronary arteries. He admitted that the coronary lesions are not always the direct result of syphilitic disease although apparently more frequent in those with syphilitic lesions elsewhere. In the absence of more patients with positive Wassermann reactions, the cardiac and arterial sequelae of syphilis may be considered to be of little importance in diabetes.

Clinical Types of Arteriosclerosis.—The importance of arteriosclerosis in diabetic patients and its predominant localization in the coronary arteries and the peripheral arteries of the lower extremities have been widely recognized. Joslin [31] has demonstrated the increasing incidence of the cardiovascular, and particularly of the cardiac, mode of death. Numerous other observers have testified to the frequency of coronary arteriosclerosis [32] and coronary thrombosis.[33]

The classification of arteriosclerosis occurring among diabetic patients has been limited pathologically to localization of the predominant sites of sclerosis. Warren [32a] also differentiated the lesions in the large arteries according to whether they were chiefly elastic or muscular, the chief lesion of the former type being atheroma, and that of the latter, medial calcification. He found the atheromatous type the outstanding one, and the intimal involvement of muscular arteries the most characteristic arterial lesion in diabetes. Aside from this, arteriosclerosis has been considered a single disease entity. Allbutt vigorously disputed this view and insisted on the necessity for a clinical differentiation of arteriosclerosis, which is not a disease but the end-result in the arteries of many varied influences. He described two clinical types which are of interest here, namely, decrescent or degenerative arteriosclerosis and hyperpiesis.[34] A less confusing name for the latter is diffuse hyper-

30. Warthin, A. S.: The Rôle of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis and of Sudden Cardiac Death, Tr. A. Am. Physicians **45**:123, 1930.

31. Joslin,[15b] p. 676.

32. Warren,[4] pp. 124 and 148. Wilder, R. M.: Necropsy Findings in Diabetics, South. M. J. **19**:241, 1926. Von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, ed. 5, Berlin, A. Hirschwald, 1910, p. 189. Blotner, H.: Coronary Disease in Diabetes Mellitus, New England J. Med. **203**:709, 1930. Root, H. F., and Graybiel, A.: Angina Pectoris and Diabetes Mellitus, J. A. M. A. **96**:925 (March 21) 1931. Nathanson.[8]

33. (*a*) Joslin, [15b]. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8**:245, 1929.

34. Allbutt, T. C.: Arteriosclerosis: A Summary View, New York, The Macmillan Company, 1925; Diseases of Arteries Including Angina Pectoris, New York, The Macmillan Company, 1915.

plastic sclerosis.[35] A third common clinical type of arteriosclerosis has also been described. It has been variously named malignant arteriolosclerosis, malignant hypertension,[36] the malignant phase of essential hypertension[37] and malignant nephrosclerosis.[38] Diabetes is rare in association with this clinical type of arterial lesion.

One hundred cases in this series have been classified in accordance with the descriptions of these types of arteriosclerosis. Under degenerative arteriosclerosis are included all cases in which the heart was normal or only slightly enlarged; under diffuse hyperplastic sclerosis, those in which the heart was enlarged. Among the latter are included 3 cases without hypertension in which the large heart was considered evidence of preexisting hypertension. The cases of degenerative arteriosclerosis have been further differentiated by the presence or

TABLE 7.—*Sex Distribution by Clinical Type of Arteriosclerosis in One Hundred Cases*

Type of Arteriosclerosis	Male	Female	Total
Degenerative arteriosclerosis without hypertension	17	20	37
Degenerative arteriosclerosis with hypertension	2	43	45
Diffuse hyperplastic sclerosis	3	15	18

TABLE 8.—*Age Distribution by Clinical Type of Arteriosclerosis in One Hundred Cases*

Type of Arteriosclerosis	40 to 49 Years	50 to 59 Years	60 Years and Over
Degenerative arteriosclerosis without hypertension	16	9	12
Degenerative arteriosclerosis with hypertension	14	9	22
Diffuse hyperplastic sclerosis	3	7	8

absence of hypertension. The age and sex distribution of the clinical types of arteriosclerosis is shown in tables 7 and 8.

The most frequent clinical type of arteriosclerosis associated with diabetes is degenerative arteriosclerosis (82 per cent). Diffuse hyperplastic sclerosis is much less frequent (18 per cent), and there were no patients in this series with malignant arteriolosclerosis. Slightly more than one half of the patients with degenerative arteriosclerosis, mostly women, had hypertension (55 per cent). The age distribution indi-

35. Evans, G.: A Contribution to the Study of Arteriosclerosis, Quart. J. Med. **14**:215, 1921.

36. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

37. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930.

38. Klemperer, P., and Otani, S.: Malignant Nephrosclerosis (Fahr), Arch. Path. **11**:60 (Jan.) 1931.

cates a rather high incidence of diffuse hyperplastic sclerosis in the persons in the sixth decade. In persons in the fifth decade many cases of mild arteriosclerosis are included under degenerative arteriosclerosis.

The clinical type of arteriosclerosis bears a direct relationship to the percentage of cases of severe diabetes with which each type is associated (table 9). One half of the cases of degenerative arteriosclerosis without hypertension, and almost two thirds of those of degenerative arteriosclerosis with hypertension were in persons with mild diabetes. Four fifths of the cases of diffuse hyperplastic sclerosis were in persons with mild diabetes.

Table 10 shows the relation of retinal arteriosclerosis, aortic arteriosclerosis, retinitis and abnormal electrocardiograms to the clinical type

TABLE 9.—*Percentage Incidence of Severe Diabetes by Clinical Type of Arteriosclerosis*

Type of Arteriosclerosis	Incidence of Severe Diabetes
Degenerative arteriosclerosis without hypertension	49%
Degenerative arteriosclerosis with hypertension	38%
Diffuse hyperplastic sclerosis	18%

TABLE 10.—*Percentage Incidence of Cardiovascular Abnormalities by Clinical Type of Arteriosclerosis*

Type of Arteriosclerosis	Retinal Arterio-sclerosis	Aortic Athero-sclerosis, Grades 1, 2 and 3	Aortic Athero-sclerosis, Grades 2 and 3	Retinitis	Abnormal Electro-cardiogram T_{12} and Conduction Defects
Degenerative arteriosclerosis without hypertension	36%	61%	39%	14%	26%
Degenerative arteriosclerosis with hypertension	72%	77%	66%	23%	29%
Diffuse hyperplastic sclerosis	93%	94%	88%	43%	65%

of arteriosclerosis. The lowest incidence of each of these variants occurred in persons with degenerative arteriosclerosis without hypertension. In persons with degenerative arteriosclerosis with hypertension, the percentages were consistently higher, and in those with diffuse hyperplastic sclerosis they were highest. The same relationship to the clinical type of arteriosclerosis is demonstrated in the incidence of cardiac symptoms, cardiac decompensation, cardiac pain of all types and angina pectoris (table 11). These two tables indicate that the frequency of clinically recognizable arteriosclerosis in the retina and aorta, retinitis, abnormalities of the electrocardiogram and cardiac symptoms, including pain and cardiac decompensation, bears a direct relation to the clinical type of arteriosclerosis as determined by the size of the heart and the blood pressure.

EVALUATION OF CARDIOVASCULAR ABNORMALITIES

Gangrene of the lower extremities may be taken as prima facie evidence of severe arteriosclerosis, not only in the arteries of the leg but in the coronary and other important vascular branches. Cerebral or coronary thrombosis has the same significance. The presence of the last mentioned condition indicates the most probable mode of death, but the presence of widespread vascular lesions may lead a patient with gangrene of the foot, successfully treated, to a fatal end through closure of the cerebral or coronary arteries. Any combination of these terminal events is possible in the diabetic patient who avoids the pitfalls of coma and infection until an advanced age. The management of the arteriosclerotic patient who also has diabetes requires an evaluation of the extent, severity and type of the arterial pathologic condition.

The severity of aortic atherosclerosis and the presence of dilatation or calcification afford a fairly reliable index of the severity of the general vascular disease. The same is true of the extent of calcification

TABLE 11.—*Percentage Incidence of Cardiac Symptoms, Cardiac Decompensation, Cardiac Pain and Angina Pectoris by Clinical Type of Arteriosclerosis*

Type of Arteriosclerosis	All Cardiac Symptoms	Cardiac Decompensation	Cardiac Pain	Angina Pectoris
Degenerative arteriosclerosis without hypertension	24%	0%	5%	0%
Degenerative arteriosclerosis with hypertension	51%	13%	18%	11%
Diffuse hyperplastic sclerosis	67%	17%	39%	22%

of the arteries of the lower extremities. It is somewhat more difficult to grade the severity of retinal arteriosclerosis, and it is questionable whether, aside from determining the presence or absence of the condition, this would be useful in determining the state of the general arterial tree. All these evidences of general vascular diseases are frequent in elderly diabetic patients, and it sometimes is difficult to deduce from them in more than general terms any prognostic conclusions. A more valuable guide is the clinical type of arteriosclerosis. The general arterial disease is more widespread and, consequently, of greater importance in diffuse hyperplastic sclerosis than in degenerative arteriosclerosis, and in the latter type of cases, those with hypertension are more likely to be accompanied by cardiac sequelae.

Nathanson [3] has shown that the incidence of coronary sclerosis is directly proportional to the size of the heart. The clinical determination of the type of arteriosclerosis, based as it is chiefly on cardiac enlargement, consequently indicates the relative importance of arteriosclerosis in the coronary arteries and, by that token, also of general arteriosclerosis.

Significance of Retinitis.—The prognostic significance of arteriosclerotic retinitis depends on the clinical type of arteriosclerosis in which

it is found and, more importantly, on the presence or absence of diabetes. In the nondiabetic patient, Moore [8] demonstrated its association with the cerebral mode of death. This association applies particularly to diffuse hyperplastic sclerosis and, to some extent, to degenerative arteriosclerosis. In malignant arteriolosclerosis, in which retinitis and also papilledema are almost invariably present, the terminal events are more likely to be uremic or cardiac. Keith, Wagener and Kernohan [36] reported that frequently combinations of uremic, cerebral and cardiac events closed the clinical picture. In cases of diabetes with arteriosclerosis the most frequent modes of death (excluding coma and infection) are cardiac failure and coronary thrombosis. Retinitis may be considered, by virtue of its origin, as an indicator of this type of cardiovascular end in the diabetic patient. Actually, it indicates that the general pathologic condition of the entire arterial tree is severe.

The linking of retinitis to the general vascular disease in cases of diabetes does not, however, exclude a subsidiary link to the disturbance of carbohydrate metabolism. Retinitis not only increases in frequency with age and the coincident increase in vascular disease, it is more frequent in severe than in mild cases of diabetes and in cases of long duration. It is also a reversible phenomenon. In 4 cases in this series, hemorrhages and even so-called areas of retinal degeneration disappeared under observation. These factors may be summarized as follows: age and an advancing pathologic condition of the arteries predispose to retinitis; the disturbance of carbohydrate metabolism, particularly if poorly controlled, initiates it.

Significance of the Abnormal T Wave in the Electrocardiogram.—The important electrocardiographic abnormalities observed in patients with diabetes are defects in conduction (widening of the QRS complex and prolonged auriculoventricular conduction time) and anomalies of the T wave. Of these, the aberrations of the T wave are more frequent. The minor notches and slurs of the QRS complex which have been reported [39] may be disregarded, and the prognostic value of low voltage Q R S and deep Q_3 are still questionable. What is known of the physiologic processes involved in the production of abnormalities of the T wave throws little light on their relation to diabetes. Lewis [40] dismissed the subject with a footnote. Katz [41] has shown that the anomalies are

39. Blitzsten, E. P. W., and Schram, D. L.: Diabetes: Electrocardiographic Studies, Arch. Int. Med. **36**:770 (Dec.) 1925.

40. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1925, p. 122.

41. Katz, L. N.: The Significance of the T Wave in the Electrogram and the Electrocardiogram, Physiol. Rev. **8**:447, 1928.

not pathognomonic of any clinical entity. Ordinarily, they are said to signify myocardial disease or coronary disease, but these are vague terms and far from helpful. The so-called coronary T wave is not found exclusively in coronary disease; conversely, coronary arteriosclerosis may be present without the cove-shaped T wave or without the T_1 or T_3 type of disturbance of the S T segment, and in fact without any abnormality of the T wave. The expressions "myocardial disease" and "coronary disease" as applied to changes of the T wave cover a wide range of possible anatomic and physiologic variations, some not at all related to the heart. Furthermore, many of these abnormalities are reversible, even without coronary thrombosis. For these reasons, the interpretation of an abnormal T wave depends on the clinical milieu in which it is found. In cases of diabetes, the abnormal T wave and conduction defects are found under the following circumstances:

1. In diabetic coma, dehydration affects the skin capacity so that electrocardiograms are so distorted as to make it frequently impossible to ascertain whether or not the T wave is normal. In addition to these changes, Faulkner and Hamilton [42] reported 2 cases of abnormal T wave in 15 cases of coma. One of the patients recovered and later had a normal control record. They also noted that in 3 cases in which the electrocardiogram was normal during coma it was abnormal later.

2. In hypoglycemic states, minor changes are found, with subsequent restitution to normal.[43]

3. Infection may produce changes in the electrocardiogram. Case 112 illustrates this. In 1931, the electrocardiogram was normal. In 1932, pulmonary tuberculosis was reactivated, with coincident diminution of carbohydrate tolerance and the appearance of an abnormal T wave in lead II. The flat T_1 wave in case 9 may also be due to infection. Similar temporary aberrations occur in many acute infections in nondiabetic cases.

4. Temporary abnormalities appear in phases of the loss of carbohydrate tolerance when uncontrolled and without any other complicating factor. Smith and Hickling [44] described increases in amplitude of the upright T wave after dietetic standardization, chiefly in young patients. They also reported 2 cases of T_{12} inversions which came upright, one

42. Faulkner, S. M., and Hamilton, B. E.: The Electrocardiogram in Diabetic Coma, Am. Heart J. **8**:691, 1933.

43. Middleton, W. S., and Oatway, W. H.: Insulin Shock and the Myocardium, Am. J. M. Sc. **181**:39, 1931. Soskin, S.; Katz, L. N.; Strouse, S., and Rubinfeld, S. H.: Treatment of Elderly Diabetics with Cardiovascular Disease, Arch. Int. Med. **51**:122 (Jan.) 1933.

44. Smith, K. S., and Hickling, R. A.: Electrocardiographic Changes During Treatment of Severe Diabetes, Lancet **1**:501, 1932.

in a few weeks and the other after fifteen weeks. Cases 21 and 28 illustrate similar changes. Neither patient had infection or cardiac symptoms. In the first, the elevation of the T wave was progressive, requiring one year; in the second, admitted in a precomatose state, the change occurred after one week in the hospital.

5. The most frequent cause of electrocardiographic abnormalities is arteriosclerosis and its sequelae. The cases due to dehydration, infection, hypoglycemia or loss of carbohydrate tolerance are few in comparison with the many in which the cause is directly related to the arterial pathologic condition. This has already been indicated in the data presented, which may be summarized as follows: The incidence of electrocardiographic abnormalities increases with age; like retinitis, they are only slightly more frequent in females than in males; no direct relationship could be demonstrated to either the severity or the duration of diabetes, and the incidence is directly related to the clinical type

TABLE 12.—*Percentage Incidence of Abnormal Electrocardiogram by Clinical Type of Arteriosclerosis and Cardiac Sequelae*

Type of Arteriosclerosis	Without Cardiac Symptoms	With Cardiac Symptoms	With Cardiac Decompensation	With Cardiac Pain	With Angina Pectoris
Degenerative arteriosclerosis without hypertension	22%	38%	No cases	0%	No cases
Degenerative arteriosclerosis with hypertension	18%	39%	57%	50%	50%
Diffuse hyperplastic sclerosis	20%	75%	100%	80%	75%

of arteriosclerosis. Two other facts are pertinent: In 7 cases (cases 10, 31, 83, 87, 104, 116 and 120), an abnormal electrocardiogram appeared while the patient was under observation, when under good conditions of metabolic control and without any complicating infection. In 4 other cases (cases 24, 76, 94 and 112) there was a complicating infection. In the 7 cases in which arteriosclerosis alone was involved, none of the patients had coronary thrombosis. The appearance of the abnormal electrocardiogram was associated with cerebral thrombosis in case 10 and with progressive loss of vision due to retinitis in case 31. Finally, it should be noted that abnormal electrocardiograms are found in about one fifth of the cases in which there are no cardiac symptoms (table 12). With cardiac symptoms and decompensation, the percentages increase; and with retinitis, abnormal electrocardiograms are two and one-half times as frequent as without retinitis.

6. Abnormalities of the T wave may also be due to factors as yet unknown, possibly in association with disturbances of the autonomic nervous system.

To summarize, abnormal T waves in cases of diabetes are seen under the following conditions: infection, disturbances of carbohydrate and water metabolism and general arteriosclerosis (including coronary sclerosis and thrombosis). The changes due to the first two conditions may be transient. They are probably the result of reversible processes in the cardiac muscle or neuromuscular tissues. Changes due to advanced arteriosclerosis are irreversible, both pathologically and in the electrocardiogram. Excluding the transient abnormalities of the T waves due to causes other than coronary thrombosis, electrocardiographic abnormalities should be considered evidences of advanced general arteriosclerosis. In this respect, the significance of the abnormal electrocardiogram is similar to that of retinitis.

SUMMARY AND CONCLUSIONS

1. In a series of 120 cases of diabetes mellitus in persons above the age of 39, arteriosclerosis was demonstrable by clinical methods in the aorta in 75 per cent of the patients, of whom 60 per cent had aortic dilatation, in the retinal arteries in 69 per cent, in either the aorta or the retina in 89 per cent, and in both in 51 per cent.

2. The heart was enlarged in 47 per cent of the cases, but in only 18 per cent was the enlargement more than slight. Cardiac enlargement is less frequent in patients with diabetes past the fourth decade of life than in nondiabetic patients with arteriosclerosis.

3. Hypertension was present in 56 per cent of the cases but was transient in all but 38 per cent; retinitis occurred in 28 per cent of the cases, and electrocardiographic abnormalities (T wave abnormalities and conduction defects), in 35 per cent.

4. After the fourth decade of life, female diabetic patients outnumber the male patients two or three times.

5. Nine tenths of all diabetic patients live at ages at which they are exposed to the risk of arteriosclerosis from causes other than diabetes.

6. Cardiovascular abnormalities in diabetic patients after the fourth decade are more frequent in females than in males.

7. The incidence of retinitis, retinal arteriosclerosis, aortic arteriosclerosis, hypertension and abnormalities of the electrocardiogram increases with age.

8. The incidence of cardiac enlargement diminishes abruptly after the sixth decade.

9. Retinitis is more frequent in cases of severe than in those of mild diabetes.

10. Retinitis is more frequent in cases of diabetes of long than in those of short duration.

11. Diabetic patients with severe arteriosclerosis and a high incidence of cardiovascular abnormalities, other than retinitis, tend to have mild diabetes.

12. Arteriosclerotic patients of advanced ages whose diabetes is of recent origin tend to have a higher incidence of cardiovascular abnormalities than those of the same age group in whom diabetes began earlier.

13. Rheumatic fever and syphilis are minor factors in the development of cardiovascular disease in diabetic patients.

14. Diabetic patients with arteriosclerosis have two distinctive types of arteriosclerosis: Most of them have degenerative arteriosclerosis, and a small percentage have diffuse hyperplastic sclerosis.

15. Among patients with degenerative arteriosclerosis without hypertension there are as many with mild as with severe diabetes; in those with degenerative arteriosclerosis with hypertension, the mild cases predominate; of those with diffuse hyperplastic sclerosis, four fifths have mild diabetes.

16. The incidence of all cardiovascular abnormalities studied is highest in patients with diffuse hyperplastic sclerosis, lower in those with degenerative arteriosclerosis with hypertension and lowest in those with degenerative arteriosclerosis without hypertension. The clinical type of arteriosclerosis also determines the incidence of cardiac symptoms and sequelae.

17. Retinitis and the abnormalities of the electrocardiogram are chiefly indexes of an advanced arterial pathologic condition in the choroidal and coronary arteries, but other factors are also involved in determining their initiation. Clinically, the presence of these abnormalities usually signifies advanced general arteriosclerosis.

SECRETION OF MUCUS AND ACID BY THE STOMACH IN HEALTHY PERSONS AND IN PERSONS WITH PEPTIC ULCER

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The importance of gastric mucus as a neutralizer of gastric acidity and as a protective coating mechanism has been stressed by Heidenhain,[1] Pavlov [2] and his school, Zweig,[3] Webster,[4] Bolton and Goodhart,[5] Fogelson,[6] Kim and Ivy,[7] Babkin and Komarov [8] and a number of other workers.[9] Differing views have recently been advanced by Bonis,[10] Kalk and Bonis [11] and Mitchell.[12]

The work reported here was undertaken in order to find how much visible mucus and acid is secreted by persons suffering from peptic ulcer as compared with that secreted by normal persons. It was thought that a difference in the amount of mucus secreted by the two groups might be indicative of the protective mechanism of mucus against autodiges-

This investigation was aided by a grant from the Louis L. Cohen Fund.

A preliminary report was read before the American Physiological Society, New York, March 29, 1934.

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1. Heidenhain, R., in Hermann, L.: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, 1883, vol. 5, p. 122.

2. Pavlov, I. P.: The Work of the Digestive Glands, London, C. Griffin & Company, 1910.

3. Zweig, W.: Arch. f. Verdauungskr. **12**:364, 1906.

4. Webster, D. R.: Am. J. Physiol. **90**:718, 1929.

5. Bolton, C., and Goodhart, G. W.: J. Physiol. **73**:115, 1931; **77**:287, 1933.

6. Fogelson, S. J.: Treatment of Peptic Ulcer with Gastric Mucin, J. A. M. A. **96**:673 (Feb. 28) 1931.

7. Kim, M. L., and Ivy, A. C.: Prevention of Experimental Duodenal Ulcer by Feeding Neutral Gastric Acid, J. A. M. A. **97**:1511 (Nov. 21) 1931.

8. Babkin, B. P., and Komarov, S. A.: Canad. J. M. A. **27**:463, 1932.

9. Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1928, p. 364.

10. Bonis, A.: Ztschr. f. klin. Med. **113**:611, 1930.

11. Kalk, H., and Bonis, A.: Deutsches Arch. f. klin. Med. **173**:53, 1932.

12. Mitchell, T. C.: J. Physiol. **73**:427, 1931.

tion of the stomach or the first part of the duodenum. The improbability of a protection of the duodenum by antitrypsin has been demonstrated in earlier papers.[13]

Gastric mucus is secreted by the cylindric surface epithelium [1] and by the mucoid cells in the tubular glands.[14] Most gastric juices contain two varieties of mucus, one of which has a visible form, which frequently assumes a threadlike appearance in a fresh specimen of gastric contents and often forms lumps. This mucus usually contains a higher amount of pepsin than the supernatant gastric juice.[15] The high pepsin content and the threadlike structure suggest that it is secreted by the mucoid cells in the tubular glands. The second form of mucus found in gastric juice is in solution and may be precipitated by various means.[16] According to Webster and Komarov,[16] the two types of mucus are chemically different; the visible mucus is secreted by the surface epithelium, while the dissolved mucus originates from the glandular part of the stomach.

It is known from the work of Pavlov [2] and others that a variety of substances increase the mucus secreted by the stomach.[9] Bread and a number of other substances that act physically or chemically, like hot water, alcohol, silver nitrate and volatile oil of mustard, or secretagogues, like pilocarpine, belong to this group.

METHODS AND MATERIAL

Method.—Pilocarpine was chosen to stimulate the secretion of mucus in order to avoid the introduction of material into the stomach. Four milligrams of pilocarpine nitrate was injected subcutaneously. Salivation, lacrimation and flushes occurred in most instances, but no untoward effects were observed. A Rehfuss tube, swallowed by the patient, was connected through a bottle to suction which was kept constant between 6 and 8 cm. of mercury by a manometer and a needle valve. Another Rehfuss tube was put into the mouth of the subject and connected to a second bottle with suction, to remove saliva (the subjects were instructed not to swallow any). Every ten minutes the bottle with the gastric contents was removed and put into an icebox immediately. There were four ten minute periods before the injection of pilocarpine and six (a number of times, eight) after it. Each specimen of a ten minute aspiration was put into a graduate centrifuge tube and centrifugated at 1,600 rotations per minute for ten minutes. The amount of visible mucus was read and 1 cc. samples of the supernatant gastric juice taken for the titration of free and combined acid. In a number of tests the acidity of the visible mucus was titrated also, and chlorine was determined in mucus and supernatant juice.

13. Necheles, H.; Ling, J., and Fernando, F.: Am. J. Physiol. **79**:1, 1926. Necheles, H., and Fernando, F.: ibid. **79**:9, 1926. Necheles, H.: Chinese J. Physiol. **2**:229, 1928.

14. Lim, R. K. S.: Quart. J. Micr. Sc. **66**:187, 1922.

15. Brestkin, M. P., and Bickoff, K. M.: J. russe de physiol. **7**:301, 1924; quoted by Babkin, p. 365.[9]

16. Webster, D. R., and Komarov, S. A.: J. Biol. Chem. **96**:133, 1932.

The large amount of data obtained in these studies was treated statistically by the method of R. A. Fisher,[17] to determine whether the differences denoted real experimental differences rather than accidental biologic variation. In this statement a P value of 0.05 or less is considered to indicate that the variation observed is experimentally significant.

Subjects.—Our normal subjects were university students and unemployed from the unemployment relief agency. While we considered the former as reliable as our own patients with regard to their history of the use of alcohol, we suspected that part of the latter group indulged in excessive drinking, and in the results we have been careful to look for evidence of alcoholism. The patients were from Mandel Clinic of Michael Reese Hospital and had an established history as well as clinical, laboratory and roentgen evidence of duodenal ulcer. While some histories

TABLE 1.—*Subjects of Test for Visible Mucus and Gastric Acidity*

	Number of Subjects	Age Group, Years	Average Age, Years
Normal persons			
Nondrinkers under 40 years of age	19	18 to 40	25
Nondrinkers over 40 years of age	8	42 to 53	49
Drinkers, all ages	10	31 to 51	40
	37		
Patients			
Nondrinkers under 40 years of age	9	20 to 39	32
Nondrinkers over 40 years of age	6	42 to 52	47
Drinkers, all ages	9	33 to 51	45
	24		

TABLE 2.—*Duration of Symptoms*

	Duration of Symptoms			
	3 Months to 1 Year	1 to 5 Years	6 to 10 Years	11 to 15 Years
Number of patients	4	10	6	4

were only of from three to eight months' duration, the greater number of patients had a chronic condition. All tests were done in the morning on an empty stomach, no food having been taken for fourteen hours and no heavy meal for twenty hours.

We divided our subjects into two groups, those below and those above 40 years of age, because, according to the statistics of Vanzant, Alvarez, Eusterman, Dunn and Berkson,[18] this age is approximately the dividing line above which gastric acidity in males begins to decline. The normal subjects were white men, except for two Negroes. The patients were all white men, except for two white women, observations on whom were included with those on the men, as there were no evident significant differences.

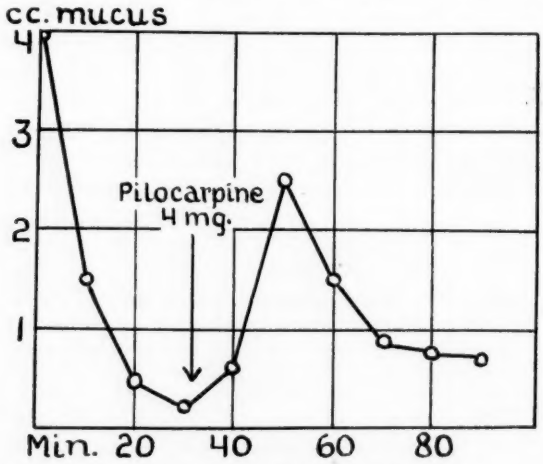
17. Fisher, R. A.: Statistical Methods for Research Workers, New York, Oxford University Press, 1926, p. 105.

18. Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, A. L., and Berkson, J.: The Normal Range of Gastric Acidity from Youth to Old Age, Arch. Int. Med. **49**:345 (March) 1932.

RESULTS

Secretion of Mucus.—The nature of the visible mucus makes it necessary to combine several samples taken consecutively. The mucus usually comes in threads and clumps, and sometimes one gets no mucus at all in one sample and a great deal in the next. This is probably due to the method of aspiration. Since the mucus clumps and is not evenly distributed throughout the gastric contents, more may be aspirated during one ten minute period than during the other. The average mucus content of more than one period is therefore more apt to represent the correct figure.

The resting stomach contains mucus, and since the night secretion of acid and mucus by the stomach may be of more importance in case



Secretion of mucus in normal subjects.

of ulcer than the day secretion (which is mostly neutralized by food), the volume of mucus of the first two control tests was taken into consideration. In practically all tests, the amount of mucus of the first two control periods was higher than that of the following two control periods, which usually were of the same order of magnitude. Ten minutes after the injection of pilocarpine the volume of mucus usually is not much different from that of the preceding two periods (controls 3 and 4), but from twenty to fifty minutes after the injection of pilocarpine there is an increase of the mucus in the aspirated gastric juice. Sixty and seventy minutes after the injection of pilocarpine the volume of mucus usually returns to the level of the two last controls. The chart illustrates what we found to be typical for many of our tests on normal subjects.

In the Resting Stomach in the Morning: The combined volumes of mucus of the first two control periods show a significant increase with age in normal persons who are not habitual consumers of alcohol ($P<0.05$). The means are 6.31 cc. of mucus in persons below 40 years of age and 10.04 cc. in persons above 40 years of age. Patients with ulcer who do not drink alcohol do not show this increase of mucus with age ($P>0.4$). The means are 5.92 cc. of mucus in patients below 40 years of age and 7.25 cc. in patients above 40 years of age. While the means of the normal persons appear to be higher than those of the patients with ulcer, statistically there is no significant difference between the volume of mucus of the group of normal persons and the group of patients with ulcer.

Normal persons who are habitual consumers of alcohol and nondrinkers have the same amount of mucus. Drinkers with ulcer have a greater amount of mucus than nondrinkers with ulcer (the means are 12.3 versus 7.25 cc.). This is indicative of associated gastritis in the case of the patients with ulcer who drink alcohol.

Before and After Injection of Pilocarpine: While the two age groups of normal subjects and patients had doubtful changes after the injection of pilocarpine, the combined groups of normal subjects and of patients showed a difference. Twenty-seven normal persons who did not consume alcohol had an increase of 0.7 cc. of secretion of mucus after the injection of pilocarpine ($P = 0.05$), and fifteen patients with ulcer who did not drink had only 0.1 cc. ($P > 0.6$). The means of the differences are (in cubic centimeters):

	Before	After	Difference
Normal persons	1.98	2.7	+0.72
Patients with ulcer	1.33	1.46	+0.13

This shows that normal persons have an increase of secretion of mucus after the injection of pilocarpine and that patients with ulcer have none. The group of normal drinkers (all ages combined) showed a borderline decrease of secretion of mucus after the injection of pilocarpine ($P = 0.54$). The mean of the difference is minus 1.5 cc. of mucus (a decrease of 1.5 cc. after the injection of pilocarpine). Since the normal nondrinkers had an increase in the secretion of mucus after the injection of pilocarpine and since the normal drinkers had a decrease, the difference between the two groups is significant ($P < 0.01$).

The free and combined acid of the mucus was usually the same as that of the supernatant gastric juice without visible mucus. Also, the values of the total chlorine of the mucus were within the limits of variation of the supernatant juice.

The clear supernatant juice of all specimens from fifteen patients was used to estimate the amount of dissolved mucus by acetone precipi-

tation.[16] No consistent results were obtained. Our observations are at variance with those of Anderson, Fogelson and Farmer.[19] Their series of four observations on two patients with ulcer and two persons with normal stomachs seems to be too small, however, to decide this question.[20]

Acidity of the Gastric Secretion.—Free Acidity of the Resting Stomach: The means of the first control samples of the groups were compared. There were no significant differences between the groups of normal persons above and below 40 years of age, whether drinkers or nondrinkers of alcohol. But in the patients with ulcer, the group above 40 years of age had a mean acid content much higher than the group of patients under 40 years of age ($P < 0.01$). The mean for the group under 40 years of age was 13 clinical degrees of free acid and that of the group above 40 years of age, 44 degrees. These results are not necessarily opposed to those of Vanzant, Alvarez, Berkson and Eusterman,[21] who found a decrease of acidity with age in patients with ulcer as well as in normal persons. Their data are based on the response of the stomach to an Ewald test meal, while ours are taken from the first sample of gastric juice withdrawn from the resting stomach in the morning. Our values may be representative of the state of secretion during rest, perhaps for the night period. From the research of Einhorn and, recently, of Winkelstein [22] and Palmer,[23] it is evident that the stomach of a patient with ulcer secretes more acid at night than does the normal stomach. Furthermore, we observed in a number of tests on patients with ulcer that, while there is free acid in the resting stomach, there is no free acid response after the Ewald test meal (one and one and a half hours afterward).

Combined Acidity of the Resting Stomach: There were either no differences between the groups or only doubtful ones.

Free Acidity Before and After Injection of Pilocarpine: The same averages were compared as in the mucus tests, i. e., the mean of tests 3 and 4 before and of tests 2 to 5 after the injection of pilocarpine. After the injection of pilocarpine the free acidity of the group of normal per-

19. Anderson, R. K.; Fogelson, S. J., and Farmer, C. J.: Proc. Soc. Exper. Biol. & Med. **31**:520, 1934.

20. Dr. Fogelson informed us recently that he verified his results in a great number of additional tests.

21. Vanzant, F. R.; Alvarez, W. C.; Berkson, J., and Eusterman, G. B.: Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases, Arch. Int. Med. **52**:616 (Oct.) 1933.

22. Winkelstein, A.: Am. J. M. Sc. **185**:695 (May) 1933.

23. Palmer, W. L.: Fundamental Difficulties in the Treatment of Peptic Ulcer, J. A. M. A. **101**:1604 (Nov. 18) 1933.

sons over 40 years of age dropped 21.1 clinical degrees (mean of the difference, $0.02 > P > 0.01$). In no other group did such a drop occur.

Combined Acidity Before and After Pilocarpine: No significant difference for any group was found. We might expect that the mean of the difference before and after the injection of pilocarpine for normal persons above 40 years of age should increase, because the amount of free acid dropped after the injection of pilocarpine. It seems as if pilocarpine causes changes in the secretion of acid and of mucus through a different mechanism.

COMMENT

We have not presented the figures for visible mucus in per cent of the total gastric juice, since that would introduce too large an error into the calculations. When the total sample of gastric juice obtained in one period is very small, the mucus (which is mostly coherent) may be recovered completely, while some of the watery fluid may escape. Statistical treatment of all results showed that there were either doubtful or insignificant changes in the percentages of the mucus in the various groups.

The mucus content of the resting stomach is certainly of interest, because it possibly represents the activity of a supposedly protective mechanism during the rest period of the stomach. This assumption is strengthened by our observations that in normal persons the amount of mucus in the resting stomach increases with age, while in patients with ulcer there is no such increase. Patients with ulcer who indulge in alcohol have a greater amount of mucus in their resting stomach than nondrinkers with ulcer. The history of drinking alcohol goes back, in most cases, before the first appearance of symptoms of ulcer. Many of the patients stopped drinking when they realized that they had disease of the stomach. A few continued to drink alcohol because it relieved the pain in the stomach. It is probable that in all or in most of the patients, gastritis was associated with the ulcer.

Normal persons show an increased secretion of mucus after the injection of pilocarpine, while patients with ulcer, drinkers and nondrinkers, do not show such an increase. The group of normal persons who drink alcohol showed a decrease of mucus secretion after the injection of pilocarpine. This lack of reactivity may explain why we found a number of habitual drinkers among patients with ulcer.

It is possible that the reaction of the gastric secretory mechanism to pilocarpine is indicative of the reaction of the stomach to a normal stimulus, like bread, for instance; that is, food provokes an increase of mucus as well as pilocarpine does. The mucus protects the stomach and duodenum physically and perhaps also chemically. Our results indicate that

in the stomach of a normal person such a mechanism is effective, but not in the stomach of drinkers or of persons with duodenal ulcer.

We do not want to attach significance to our observations on free and combined acid because, as pointed out earlier, pilocarpine may act on two different places simultaneously, on the acid secretion and on the mucus secretion.

All of our patients suffered from duodenal ulcer. Mucus from the stomach may protect this type of ulcer as well as, or even better than, an ulcer in the stomach. The reaction in the upper part of the duodenum tends to be alkaline; the solubility of the visible mucus increases, and it may infiltrate the mucosa.[24]

The choice of the age groups in this study was arbitrary, and larger groups may bring evidence of a deficiency in the mechanism of secretion of mucus before the age of 40 (duodenal ulcer occurs chiefly in younger persons). We do not want to conclude from the results that the differences in secretion of the mucus between normal persons and patients with ulcer explain the cause of ulcer. We are rather inclined to assume that the difference in secretion of mucus of the two groups may as well be due to the pathologic condition of the stomach and duodenum as to the causation of the disease.

SUMMARY

The gastric secretion of visible mucus has been measured after fasting and following the injection of pilocarpine in thirty-seven normal persons and in twenty-four patients with duodenal ulcer. The amount of visible mucus in the stomach after fasting is greater in normal persons above 40 years of age than in normal persons below 40 years of age. This increase with age does not take place in patients with ulcer.

After the injection of pilocarpine, normal persons show an increased secretion of visible mucus, while patients with ulcer (nondrinkers and drinkers of alcohol) do not show such an increase. Normal persons who drink alcohol show a decreased secretion of mucus after the injection of pilocarpine.

24. Langenskiöld, F.: Skandinav. Arch. f. Physiol. **31**:1, 1913.

DIET IN CHRONIC ARTHRITIS

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Many factors play a rôle in producing one or another form of chronic arthritis. The influence of diet has been given attention, but there have been few studies concerning its etiologic rôle. It has not been unusual to observe considerable improvement in chronic arthritis following the correction of faulty dietary habits, although frequently other therapeutic measures have been employed at the same time. The question arises of the importance of dietary factors in the causation of arthritis. An attempt is made here to reexamine the evidence for the relationship between diet and chronic arthritis, especially the possible etiologic relationship of long-continued, mildly deficient diets.

An evaluation has been made of the dietary history of seventy-five patients with chronic arthritis. There were twenty-seven patients with hypertrophic (degenerative) arthritis, forty with atrophic (rheumatoid) arthritis, and eight with what has been termed chronic infectious arthritis. Six of the latter eight cases were proved to be due to gonococcic infection, and the remaining two were tuberculous in origin. Patients with rheumatic fever and gout were rigidly excluded.

A control group of patients whose dietary habits were studied was made up of thirty persons unselected except that they came from similar social strata and were of the same age and sex distribution as the patients with arthritis. A higher percentage of patients was chosen from the clinic group advisedly. The control group included patients convalescent from lobar pneumonia, with infections of the upper respiratory tract, pulmonary tuberculosis, carbon monoxide poisoning, arterial hypertension and other disorders.

The evaluation of the various constituents of the diet was, of necessity, difficult. The caloric content of the diet of a given patient was said to be excessive when the body weight was increasing or remained considerably above that of the ideal. The diet was termed excessive in carbohydrate foodstuffs when the patient consumed approximately 600 Gm. of starch and sugar daily and lived a sedentary life, or when he derived as much as 80 per cent of the caloric content of the diet from the

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food substances just mentioned. The protein content of the diet was considered inadequate when, per week, there were not more than four servings of meat, two or three eggs, little or none of the dairy products and only occasionally a serving of vegetables, such as lentils. The nature, as well as the amount, of protein in the diet had to be evaluated.

Vitamins were considered to be deficient when, for a long period of time, foods which are recognized to supply them were scant in the diet or rarely consumed. A patient was considered to have received little of vitamin C when fresh fruits and vegetables in small amounts and animal food, rich in vitamin C, were taken but once or twice a week. When there was any reasonable doubt as to whether the diet of a patient was grossly deficient in a given vitamin, the diet was classified as being on the borderline of deficiency.

TABLE 1.—*Distribution of Subjects as to Sex, Age and Social Status*

				Sex		Age			Diet		
	Number of Cases	Private Patients	Patients from Clinic	Males	Females	Minimum	Maximum	Average	Borderline Deficient, per Cent of Cases	Deficient, per Cent of Cases	Undesirable, per Cent of Cases
Hypertrophic (degenerative) arthritis	27	11	16	5	22	40	78	56	7.4	25.9	33.3
Atrophic (rheumatoid) arthritis	40	12	28	11	29	18	60	35	37.5	12.5	50.0
Infectious arthritis	8	2	6	6	2	19	70	36	25.0	25.0	50.0
Control	30*	4	26	7	23	16	72	35	26.7	13.3	40.0
Total	105	29	76	29	76						

* The number of private patients is relatively small in the control group. This may increase slightly the percentage of undesirable diet.

In evaluating the mineral content of the diet, only instances of gross inadequacy could be considered. The diet of one patient consisted of one serving of meat, three eggs, 1 pound (0.5 Kg.) of butter, seven moderate servings of oatmeal and three or four onions a week, in addition to potatoes, white bread, jam and cake. This diet was obviously inadequate in such minerals as iron and calcium.

The designation of a diet as undesirable depended on a summation of the various factors. A diet grossly lacking in any one or several of the essential constituents was said to be deficient.

Table 1 shows the distribution of the group of patients as to sex, age and, to an extent, social status, and table 2 is the form used for recording the dietary history. Each patient was questioned carefully about his dietary habits preceding the onset of the symptoms of disease of the joints. The diet recorded was, with few exceptions, that of the patient's lifetime habits, and care was taken to note any definite changes in the diet preceding the onset of arthritis. Indeed, in the seventy-five

TABLE 2.—*Chart Used in Recording Individual Dietary Habits*

Name.....Age.....Sex.....
Address.....
Married.....Years.....Children.....
Present occupation.....
Past occupation.....
Other activities.....
.....
.....
.....

Diagnosis .....
Date .....
Hospital no. .....
Height .....
Weight .....
Av. weight .....
Cal. normal weight.....
+ or — av. normal weight
Now .....
In past .....

Social status..... Race..... Birthplace..... Lived in.....
Eats at home..... In restaurant..... Alone..... Married.....
Does own cooking.....Living conditions.....
Emotional strain.....Fatigue .....
Rises..... Retires..... Naps..... Sleeps well.....
Housework..... Play.....

Past history: .....
.....
.....
.....
Arthritis began..... Extent..... Severity.....
Joints involved .....

Family history: .....
.....
Parents', brothers' and sisters' heights and weights.....
.....
Arthritis .....

Food Habits

Typical day:
Breakfast .....
Noon meal .....
Evening meal .....
Between meals ..... Appetite.....
Regularity..... Likes..... Dislikes.....
Dieting..... Seasonal variation.....
Evidence of starch indigestion.....
Tea..... Coffee..... Cream..... Sugar.....
Alcohol..... Tobacco..... Condiments.....

Servings per week:

Meat.....	Butter.....	Bread (sliced) white.....	Ice cream.....
Fish.....	Cream.....	Bread (sliced) dark.....	Candy.....
Poultry.....	Mayonnaise.....	Crackers.....	Cake,.....
Eggs.....	Oleomargarine.....	Cereals (refined).....	Pie.....
Cheese.....	Nuts.....	Cereals (whole).....	Pudding.....
Liver.....	Lard.....	Potato.....	Pastry.....
Milk.....	Olive oil.....	Rice.....	Jams.....
	Macaroni.....		

Fruit (raw)	Lettuce.....
Fruit (cooked)	Spinach.....
Oranges	Cabbage.....
Tomatoes	Carrots.....
Vegetables (above ground).....	String beans.....
Vegetables (below ground).....	Peas.....

Past Food Habits

Childhood and youth .....
.....
.....
Recent changes .....

Type of Diet

Protein.....	Vitamins.....
Fat.....	Minerals.....
Carbohydrates.....	Calories.....

patients with chronic arthritis, the diet recorded in the history represented the type of diet consumed for more than ten years in all but four instances. Similarly, it was found that but two patients of the control group had altered their diets essentially within a corresponding period. In evaluating the information obtained it was necessary to consider the diet of "a typical day," the weekly servings of the various food substances, the food habits, the occupation and the average body weight or changes in body weight while the diet was being taken. In addition, such factors as emotional strain and the habits of life, which may indirectly influence the food consumed, were taken into account.

At best it is possible to obtain only an approximation of the contents of diets from the patients' descriptions. The various constituents were classified as (1) in excess of an apparently desirable optimum, (2) the

TABLE 3.—*Results of Study of Diet*

				Caloric Value		Vitamins			
	Number of Cases	Carbohydrate: Excessive, per Cent of Cases	Protein: Inadequate, per Cent of Cases	Excessive, per Cent of Cases	Inadequate, per Cent of Cases	Borderline, Deficient, per Cent of Cases	Deficient, per Cent of Cases	Total Deficient, per Cent of Cases	Minerals: Deficient, per Cent of Cases
Hypertrophic (degenerative) arthritis	27	52	3.3	59.0	3.7	3.7	23.0	26.7	18.5
Atrophic (rheumatoid) arthritis	40	60	5.0	35.0	20.0	20.0	22.5	42.5	15.0
Infectious arthritis	8	75	0.0	37.5	12.5	12.5	37.5	50.0	25.0
Control	30	63	7.4	43.0	3.3	20.0	13.3	33.3	17.0
Total	105								

optimum, (3) borderline deficient and (4) deficient for the given person. The proportion of undesirable diets in all groups was surprisingly similar, as shown in table 1.

The duration and the extent of the arthritis were estimated at the time of examination. No correlation could be established between the adequacy of the diet and the duration and extent of the disease process. As was to be expected, the poorer diets in general were those of persons of obviously poor social status. However, poor diets were found in one fourth of the patients whose financial circumstances were good.

As a diet may be termed unsatisfactory in a number of ways, certain essential constituents and relationships were considered critically. Careful consideration was given to excess of carbohydrates, protein deficiency, total caloric content and vitamin and mineral content. The results of the study are recorded in table 3.

It can be seen that there was no striking single abnormality in the diets of any one group of patients with chronic arthritis. The percentage of patients who had for years consumed grossly excessive amounts of carbohydrate foodstuffs did not vary appreciably in any

group of patients with chronic arthritis or differ from that of the control group. Diets of caloric value excessive for the individual subject were encountered in a greater number of the patients with hypertrophic arthritis than in the other groups. It was expected that this would be the case; hypertrophic arthritis is recognized as occurring more frequently in patients who are overweight than underweight. Patients who had atrophic arthritis had been receiving diets of obviously inadequate caloric content in slightly larger numbers than the other groups. The percentage of patients with atrophic arthritis who took an insufficient amount of vitamins, whether of one or of several, over a number of years, was somewhat greater than in the other groups. However, when the vitamins were considered individually, it was obvious that no one vitamin was concerned. Indeed, as is usually the case in man when a deficiency of vitamins is found, there is a deficit of several vitamins rather than of only one. In considering the mineral constituents of the diet, calcium, phosphorus, iron, sodium, potassium and iodine received attention. Gross inadequacies of one or of several of these minerals were present in approximately one sixth of the patients. As with the vitamins, several minerals rather than one alone were present in insufficient quantities. The percentage of diets inadequate in minerals was not significantly greater in one group of patients than in another.

The rôle of certain dietary constituents in the etiology of arthritis may be approached in another manner. A few careful studies of the diets and diseases common to certain tribes and nationalities might cast light on the question. Muley [1] reported but few cases of chronic arthritis in Turkey, where the diet is low in protein and high in carbohydrates and vitamins. Orr and Gilks [2] made an interesting study of the diets of two African tribes. Rheumatoid arthritis is a common disease among members of the tribe whose diet consists chiefly of protein and fat and is rich in calcium salts. On the other hand, diseases of the joints are uncommon in the tribe whose dietary is poor in calcium and whose caloric needs were supplied in the main by carbohydrate substances. Deformities of the bone and the teeth were, however, seen in the latter tribe.

We are not concerned here with the question of the ability of the patient with chronic arthritis to absorb or to utilize the dietary carbohydrates.

Patients with chronic arthritis who are undernourished may show improvement with the establishment of better nutrition. This has been accomplished in many ways, by including a diet liberal in carbohydrate

1. Muley, K.: Ernährung in Ost und West, Ztschr. f. Ernähr. **1**:361, 1931.

2. Orr, J. B., and Gilks, J. L.: Studies of Nutrition: The Physique and Health of Two African Tribes, Medical Research Council, Spec. Rep. Ser. 155, London, His Majesty's Stationery Office, 1931, p. 82.

with or without the administration of insulin.[3] The contention that a diet per se high in carbohydrate predisposes the subject to arthritis is not borne out by these studies. Diets containing an excess of carbohydrate foodstuffs are not found in any greater number among persons known to have arthritis, as compared with a control group, than among patients with diabetes. Chronic arthritis is uncommon in some tribes whose diet has been high in carbohydrates for generations.

The various vitamins have likewise been incriminated. Results of experiments on animals have suggested that a deficiency of several of the vitamins may be related to the susceptibility to and the defense against infection. The recent observations of Rinehart and Mettier [4] have pointed out the occurrence of lesions of the joints in animals which were fed a diet deficient in vitamin C and in which an infection was induced. The characteristics of the lesions observed by these workers are those occasionally seen in patients with scurvy, and are fundamentally different from those found in arthritis. The presence of infection seems only to have increased the severity of the scorbutic process.

On the basis of experiments on animals intestinal changes have been said to occur following a diet deficient in vitamin B.[5] Fletcher [6] reported that the abnormalities of the intestine in patients with chronic arthritis change toward normal with the administration of vitamin B concentrates. Haft,[7] in a carefully controlled study, concluded that the abnormalities of the intestines of patients with chronic arthritis were a manifestation of chronic illness and that they were not peculiar to this disease. Nissen [8] would attribute colonic abnormalities in chronically ill patients, as seen in chronic arthritis and rheumatic heart disease, to a functional basis. He observed improvement without alteration in the

3. (*a*) Howitt, F. D., and Christie, W. F.: The Malnutrition Factor in Rheumatoid Arthritis, Lancet **2**:1282, 1931. (*b*) Eaton, E. R., and Love, J.: Chronic Arthritis: A Study of the Dietary of Five Hundred Patients, with Results of an Experimental Course of Insulin Treatment in Twenty-Two Cases of Malnutrition, J. Am. Inst. Homeop. **26**:404 (June) 1933. (*c*) Dawson, M. H.: Report of the Second Conference on Rheumatic Diseases, J. A. M. A. **101**:1264 (Oct. 14) 1933.

4. Rinehart, J. F., and Mettier, S. R.: The Joints in Experimental Scurvy and in Scurvy with Superimposed Infection, with a Consideration of the Possible Relation of Scurvy to Rheumatic Fever, Am. J. Path. **9**:952 (Nov.) 1933.

5. McCarrison, R.: Studies in Deficiency Diseases, New York, Oxford University Press, 1921. Rowlands, M. J.: Rheumatoid Arthritis: Is It a Deficiency Disease? Proc. Roy. Soc. Med. **20**:1711 (May 25) 1927.

6. Fletcher, A. A.: Chronic Arthritis, Canad. M. A. J. **22**:320 (March) 1930.

7. Haft, H. H.: The Colonic Changes in Chronic Arthritis Compared with Other Chronic Diseases, Am. J. M. Sc. **185**:811 (June) 1933.

8. Nissen, H. A.: Atonic Stasis: Clinical and Laboratory Study of Intestinal Variations in Chronic Disease, M. Clin. North America **13**:269 (July) 1929.

vitamin allowance, but with the institution of muscle-building exercises and the addition of dietary roughage.

Vitamin D has been thought to be lacking in patients with chronic arthritis. We have found no corroboration of this in our studies. Clinical improvement may follow the administration of generous amounts of this vitamin to individual patients, yet there seems to be no justification for a conclusion as to its specific value in arthritis.

While it has been suggested that long-continued, mild vitamin deficiency may be of etiologic importance in chronic arthritis, the infrequency of arthropathy in recognized diseases of vitamin deficiency in man speaks against this. Little evidence has been offered for any direct relationship between vitamin deficiency and chronic arthritis. On examination of the evidence at hand, it seems highly improbable that such a relationship will bear critical analysis.

The mineral content of the diet seems to have no part in the onset of chronic arthritis. The calcium salts have appeared to offer the most promising angle of approach. Studies of the calcium metabolism in patients with chronic arthritis have failed to offer any grounds for speculation in this field.[9] In the tribe whose members have received little calcium for years, bony and dental deformities are rather common, but disease of the joints is rare.

The observation of clinical alterations in patients following changes in the diet should hardly be interpreted as indicative of direct etiologic significance of the constituents involved. Eaton and Love [3b] have also concluded that there seems to be little or no direct evidence that diet or any of the various dietary constituents are directly contributory to the etiology of chronic arthritis. Dietary deficiency, in the broad sense, may decrease the powers of resistance to infections. Mackie and his associates [10] found evidence suggestive of this in experiments on animals. As in tuberculosis, it has been thought that predisposition to infection and impairment of the natural responses to infection accompany faulty food habits and undernutrition. Thus the importance of a proper diet in the treatment of arthritis is not lessened. In any chronic illness dietary therapy is recognized to be of great importance. No less so in

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9. Pemberton, R., and Foster, G. L.: Studies on Arthritis in the Army Based on Four Hundred Cases: III. Studies on the Nitrogen, Urea, Carbon Dioxide Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, Arch. Int. Med. **25**:243 (March) 1920. Bauer, W.; Bennett, G. A., and Short, C. L.: Speculations on the Etiology of Rheumatoid Arthritis, New England J. Med. **208**:1035 (May 18) 1933.

10. Mackie, T. J.; Fraser, A. H. H.; Finkelstein, M. H., and Anderson, E. J. M.: The Influence of Nutrition on Susceptibility to a Bacterial Toxin, Brit. J. Exper. Path. **13**:323, 1932.

chronic arthritis is it essential to consider and to prescribe satisfactory diets, especially when altered intestinal function is present, as may be the case.

There is, of course, no standard diet for patients with chronic arthritis or with any chronic illness. The object of a diet in chronic arthritis must be to attain the optimum nutrition in the individual patient. It is necessary to consider not only a satisfactory caloric intake, whether it is to be increased or decreased, but also ample protein, vitamins and minerals and the proper relationship of the constituents to each other. Various factors inherent to the patient must also be recognized. Related diseases and disorders, particularly of the gastro-intestinal tract, food idiosyncrasies, the patient's preferences, the appetite and the economic circumstances will necessitate due care on the part of the physician. It may be advisable for the patient to be reeducated with respect to his food habits.

SUMMARY AND CONCLUSIONS

The life dietary habits of seventy-five patients with chronic arthritis and thirty patients without symptoms in the joints were studied. Fifty-nine per cent of the patients with hypertrophic degenerative arthritis had had an excess of calories in their diet for years. This is in contrast to 43 per cent of the patients of the control group. Diets of inadequate caloric content were found in 20 per cent of the patients with atrophic (rheumatoid) arthritis, as compared with 3 per cent of the control group.

Undesirable diets were encountered in the cases of one third of the patients with hypertrophic arthritis and one half of the patients with atrophic arthritis. However, the diets of 40 per cent of a control group of patients of similar ages, sex and social status were likewise poor.

No direct relationship can be established between dietary factors and the development of chronic arthritis. Neither excessive consumption of carbohydrate nor a deficiency of the various vitamins and minerals per se was found to be related to the development of chronic arthritis. The importance, however, of a good diet in the treatment of chronic arthritis, as in the treatment of any disease state, is beyond question. The diet must fit the needs of the individual patient.

THE UREA RATIO AS A MEASURE OF RENAL FUNCTION

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Tests for renal function are of two types: those that determine the power of the kidney to dilute and concentrate the urine and those that measure the ability of the kidney to eliminate the renal excretory products. Those of the first group, which includes the various tests for specific gravity, are well established and adequate; those of the second are not completely satisfactory. Beside the use of the dye tests, which are not specific, the measure of renal excretion usually is attempted by a determination of the amount of urea or nonprotein nitrogen in the blood. These estimations demonstrate how much of these substances is actually retained, but not the degree of the impairment of renal function. This is especially true when the figures for the blood chemistry determinations are low; it is not then certain whether renal function is normal or impaired, since the level of the nonprotein nitrogen in the blood may have been influenced by therapeutic measures, such as diet, or by complications, such as edema or diarrhea.

In 1917, Mosenthal and Hiller [1] suggested the ratio of the urea nitrogen to the nonprotein nitrogen of the blood as an index of the amount of effectively functioning renal tissue, irrespective of the level of the blood urea. Since that time, the methods for the determination of the nonprotein nitrogen have changed; observations are presented here on the validity of the urea ratio as a test for renal function when the more recent quantitative procedures are employed.

The urea clearance test of Van Slyke [2] and his collaborators has proved to be the most satisfactory method now available for the per-

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This study was aided by a grant from the Harriet Weil Fund.

Read before the Association of American Physicians, Atlantic City, N. J., May 1, 1934.

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1. Mosenthal, H. O., and Hiller, A.: The Relation of the Nonprotein Nitrogen to the Urea Nitrogen of the Blood, J. Urol. **1**:74, 1917.

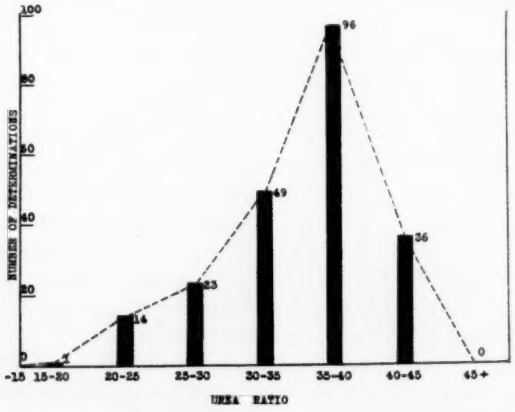
2. Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427, 1928

centage estimation of the total active renal tissue. Consequently, the urea ratio has been checked by comparison with the urea clearance values in many of these observations.

MATERIAL AND METHODS

Since 1931 more than 1,500 determinations of the urea nitrogen and the total nonprotein nitrogen in the whole blood have been carried out simultaneously on 307 persons. The patients were studied consecutively as they presented themselves in the wards and clinics of the New York Post-Graduate Hospital, in the metabolic wards of Sea View Hospital, Staten Island, and in the private practice of one of us (H. O. M.). The patients studied were grouped as follows:

1. Persons with normal renal function (laboratory workers, interns and patients with nonrenal diseases, for example, diabetes mellitus or peptic ulcer)—200 patients.



Distribution of 219 determinations of the urea ratio in 200 persons with normal renal function. The minimum urea ratio is 16.1; the maximum, 43.3.

2. Patients with Bright's disease (acute diffuse glomerular nephritis; chronic diffuse glomerular nephritis, with or without nephrotic components or uremia; focal embolic nephritis; lipoid nephrosis; amyloid nephrosis, or arteriosclerotic nephritis)—92 patients.

3. A miscellaneous group of patients with impaired renal function (surgical diseases of the kidney, for example, prostatic obstruction and renal lithiasis; chronic passive congestion due to cardiac decompensation, and dyscrasias of the blood, such as agranulocytosis, leukemia and polycythemia vera)—15 patients.

In every instance, the urea nitrogen in the whole blood was determined on the Folin-Wu filtrate by Van Slyke's gasometric urease method,[3] and the total nonprotein nitrogen, by the method of Folin and Wu.[4] The urea clearance test was

3. Van Slyke, D. D.: Determination of Urea by Gasometric Measurement of the Carbon Dioxide Formed by the Action of Urease, J. Biol. Chem. **73**:695, 1927.

4. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

carried out according to the procedure of Möller, McIntosh and Van Slyke.[2] The percentage of urea nitrogen in the total nonprotein nitrogen of the blood, termed the urea ratio, was calculated according to the formula: $\frac{100 \times \text{urea nitrogen}}{\text{nonprotein nitrogen}}$

RESULTS

Normal Value of the Urea Ratio.—In 219 determinations of the urea ratio in the blood of 200 persons with normal renal function (chart), only 1 ratio was lower than 20; the highest observed was 43.3. In the 219 observations, 145 urea ratios were between 30 and 40, indicating clearly that this was the usual figure. For practical clinical interpretations, we have considered as normal urea ratios of 44 or less.

TABLE 1.—*The Urea Ratio and Urea Clearance Values in Persons with Normal Renal Function*

		Whole Blood			
No.	Patient	Urea Nitrogen, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Ratio	Urea Clearance, per Cent of Normal
1	Bas	5.0	24.5	20.4	148.9
2	Dis	6.1	22.7	26.9	84.8
3	Bas	7.1	30.0	23.7	125.4
4	Bas	7.1	33.2	21.4	107.5
5	Bas	7.3	29.3	24.9	119.7
6	Han	7.6	30.0	25.3	151.8
7	Car	8.2	27.7	29.6	99.1
8	Car	8.7	29.3	29.7	97.3
9	Hun	8.7	29.3	29.7	100.5
10	Han	8.7	28.2	30.9	177.3
11	Car	9.1	26.7	34.1	89.9
12	Hun	9.1	27.6	33.0	115.2
13	Hun	9.1	29.5	30.9	94.1
14	Hun	9.4	26.9	34.9	89.5
15	Han	9.4	26.8	35.1	176.8
16	Han	9.7	30.3	32.0	150.9
17	Han	9.8	33.3	29.4	108.1
18	Kla	9.9	35.1	28.2	119.6
19	Han	10.0	30.5	32.8	108.3
20	Gro	10.1	25.2	40.1	141.8
21	Kla	10.1	27.3	37.0	135.2
22	Kla	10.6	31.4	33.8	107.6
23	Law	10.9	30.6	35.6	74.8
24	Bla	11.3	28.0	40.4	83.3
25	Sch	13.8	37.3	37.0	86.8
26	Osn	15.4	35.6	43.3	111.2
27	Sho	16.9	40.0	42.3	81.0

Table 1 compares the urea ratio and the urea clearance value in persons with normal renal function. The results of the two tests in this group are in entire agreement. The tendency toward a low urea ratio when the blood urea is considerably depressed is evident. This apparently is characteristic of normal persons, though it does not hold true, as will be shown later, in those with diminished renal function, in whom a low urea nitrogen is accompanied by a constantly elevated urea ratio irrespective of the fluctuations in the urea nitrogen of the blood.

The Urea Ratio with Maximal Impairment of Renal Function.—When renal activity is curtailed to the utmost, the urea ratio is usually at a level of 80 or more. This is shown in table 2, which gives the

urea ratio in 16 cases of chronic diffuse glomerular nephritis with uremic manifestations. It appears that a urea ratio of 80 indicates a maximal impairment of renal function, though a higher ratio (in one instance in this series, 91.9, table 2) may be reached.

TABLE 2.—*The Maximum and Minimum Urea Ratios Observed in Sixteen Patients with Chronic Diffuse Glomerular Nephritis with Uremic Manifestations*

No.	Patient	Number of Ratios Obtained	Whole Blood Urea Nitrogen, Mg. per 100 Cc.		Urea Ratio	
			Maximum	Minimum	Maximum	Minimum
1	Car	2	113.5	111.1	90.4	88.0
2	Sag	6	118.0	101.5	85.1	75.6
3	Riz	2	118.0	112.4	89.0	80.1
4	Roc	2	125.4	111.6	79.2	77.6
5	Flo	3	130.1	95.4	83.8	73.2
6	Tar	2	135.2	105.8	84.5	80.4
7	Sab	6	135.3	116.0	87.9	77.0
8	Ham	5	170.3	139.0	91.9	81.2
9	Ell	4	171.0	153.7	91.4	82.6
10	Gli	19	173.7	109.3	90.6	78.6
11	She	3	180.2	136.8	82.1	78.7
12	Amm	2	180.9	147.5	83.5	77.9
13	Per	2	198.9	114.8	86.4	80.2
14	Kos	3	209.2	194.5	88.9	80.9
15	Got	2	231.6	194.9	72.1	68.2
16	Ang	5	275.7	218.5	75.3	67.4

TABLE 3.—*The Urea Ratios in a Patient Aged 25, with Chronic Diffuse Glomerular Nephritis in a Preuremic State Over a Period of Seven Months, Showing the Rather Constant Maintenance of the High Ratio in Spite of the Variations That Occur in the Nonprotein Nitrogen of the Blood as the Result of Treatment*

Date	Urea Nitrogen, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Ratio	Date	Urea Nitrogen, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Ratio
1933				1933			
Feb. 4	85.7	111.1	77.1	Feb. 23	50.8	69.0	73.6
Feb. 8	80.5	93.0	86.6	Feb. 28	58.2	78.4	74.2
Feb. 9	80.2	90.5	88.6	March 4	60.9	85.1	71.6
Feb. 10	74.2	81.3	91.3	March 10	80.8	90.5	89.3
Feb. 11 a.m.	71.5	82.6	86.6	March 13	69.9	90.2	77.5
Feb. 11 p.m.	69.1	82.3	84.0	March 14	68.6	90.9	75.5
Feb. 12	67.4	75.2	89.6	March 15	63.5	90.9	69.9
Feb. 15	65.6	73.3	89.5	March 20	50.2	83.9	59.8
Feb. 16	67.1	85.8	78.2	March 28	51.0	69.8	73.1
Feb. 17	64.8	83.3	77.8	April 11	51.6	84.5	61.1
Feb. 18	63.1	83.3	75.8	April 27	89.9	110.5	81.4
Feb. 20 a.m.	59.7	78.4	76.1	Aug. 16	139.0	170.4	81.6
Feb. 20 p.m.	61.9	83.9	73.8	Sept. 2	170.3	185.3	91.9
Feb. 21	50.3	82.7	71.7	Sept. 5	163.4	197.4	82.8

In table 3 are tabulated the urea ratios in a patient with chronic diffuse glomerular nephritis who was in a preuremic state for seven months. Although the ratio was frequently 80 or above, some lower figures are shown. Presumably, the efficiency of the kidney may vary according to the amount of fluid intake, the volume of urine eliminated and other factors. These may well be responsible for certain fluctuations in the urea ratio pictured in a series of determinations of this sort.

Fluctuations in the Urea Ratio as the Result of Changes in Renal Function.—Changes in the urea ratio may occur in either an upward or a downward direction, marking a diminution or an improvement in renal efficiency. In table 4 are given the urea ratios in 4 patients with acute nephritis in whom a complete or partial functional recovery took place. The urea ratio reaches the normal level in the first 3 patients and approaches it in the fourth, indicating either complete recovery or a

TABLE 4.—*The Urea Ratios in Four Patients with Acute Diffuse Glomerular Nephritis with Complete or Partial Functional Recovery, Showing a Drop in the Ratio which Occurs to a Large Extent Irrespective of the Values of the Blood Urea Nitrogen*

Date, 1933	Urea Nitrogen, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Ratio	Comment
Patient Ban., age 10				
April 10	110.3	119.6	92.2	Acute diffuse glomerular nephritis; marked impairment of renal function
April 11	93.6	118.9	78.7	
April 13	40.6	48.4	83.9	
April 17	17.6	30.9	57.0	
April 22	14.1	37.7	37.4	Complete functional recovery
Patient Laz., age 28				
Feb. 7	19.5	31.9	61.1	Acute diffuse glomerular nephritis with nephrotic component; considerable impairment of renal function
Feb. 16	30.2	47.3	63.9	
Feb. 24	20.2	35.1	57.6	Urea clearance 28.2 per cent of normal
March 7	38.8	49.2	78.9	
March 29	24.4	38.5	63.4	Urea clearance 45.8 per cent of normal
Aug. 9	10.3	28.3	36.4	Complete functional recovery
Patient Fif., age 22				
Feb. 6	37.1	56.1	66.1	Acute diffuse glomerular nephritis; considerable impairment of renal function
Feb. 12	27.0	37.1	72.8	
Feb. 20	18.2	33.8	53.9	Urea clearance 32 per cent of normal
Feb. 28	14.9	26.2	56.9	Urea clearance 45.5 per cent of normal
March 7	12.0	23.1	52.0	
March 21	8.6	25.4	33.9	Urea clearance 66.1 per cent of normal; complete functional recovery
April 18	7.6	25.4	29.9	Urea clearance 98 per cent of normal
June 15	7.9	30.9	25.6	
Sept. 1	10.2	28.8	35.4	
Patient Riz., age 40				
1932				
Nov. 2	118.0	147.2	80.2	Acute exacerbation of chronic diffuse glomerular nephritis
Nov. 5	112.4	126.2	89.1	
Nov. 7	86.2	103.6	83.2	
Nov. 9	42.8	52.0	82.3	
Nov. 15	14.6	27.0	54.1	Urea clearance 53.6 per cent of normal
Nov. 16	14.1	24.7	57.1	Partial functional recovery

distinct improvement in the renal function; the urea ratio thus furnishes a good numerical index of the sequence of events. It is strikingly evident from this table that in many instances determinations of either the urea nitrogen or the total nonprotein nitrogen do not indicate the existence of any impairment of renal function; on the other hand, the urea ratio shows that a definite degree of renal impairment exists in the face of normal values for these constituents.

Table 5 shows how the urea ratio rises as impairment of renal function progresses over a period of almost two years. Here, the urea ratio furnishes an index of the extent of curtailment in the activity of the kidney.

Comparison of the Urea Ratio with the Urea Clearance.—The figures in table 6 are those from simultaneous determinations of the urea ratio and urea clearance in the blood of patients with Bright's disease. The cases are arranged in order of the diminishing values of urea clearance. In general, the urea ratio rises as the urea clearance value falls. While the results of the two tests are usually in agreement, they do not entirely parallel each other. It may be that each measures a somewhat different quality in renal function from that shown by the other and, consequently, the results are not always in absolute accord. However, the discrepancies between the two tests are so slight as to make it certain that if one is of value the other must be satisfactory.

TABLE 5.—*Rise of the Urea Ratio During a Period of Almost Two Years in a Patient Aged 25, with Chronic Diffuse Glomerular Nephritis, Who Died of Retention Uremia*

Date, 1930	Urea Nitrogen, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Ratio	Urea Clearance, per Cent of Normal
Dec. 22	18.5	38.9	47.6	26.2
1931				
Jan. 7	21.7	41.6	52.2	40.2
March 20	22.0	42.5	51.8	28.8
March 28	26.6	40.0	66.5	29.7
1932				
April 18	84.7	110.4	76.7	9.0
May 31	109.0	155.4	70.1	
June 3	107.1	137.0	78.2	
June 7	81.7	124.2	65.8	
June 14	93.3	116.2	80.3	
Sept. 8	111.7	157.9	70.7	
Sept. 29	153.7	186.0	82.6	
Sept. 30	164.2	186.8	87.9	
Oct. 2, a. m.	171.0	205.2	83.3	
Oct. 2, p. m.	170.8	186.8	91.4	
Oct. 3, exitus				

In some instances (cases 1, 2 and 3, table 6) the urea ratio indicates impairment of renal function whereas the value for urea clearance does not. At times, there are fluctuations in the urea ratio, which are noted in table 3 and have been discussed. Similar variations may be observed in the urea clearance values in table 5. We previously had an identical experience with this procedure.[5] The same explanation may be offered for these variations as for those in the urea ratio. Neither of the tests furnishes entirely constant results, and the changes in their results from time to time may be due to alterations in the activity of the kidney.

5. Bruger, M., and Mosenthal, H. O.: Urea Clearance Test as an Index of Renal Function: III. Studies of Patients with Bright's Disease, Arch. Int. Med. **50**:544 (Oct.) 1932.

Urea Ratio in Conditions Other Than Bright's Disease.—With mechanical obstruction to the urinary flow (renal calculus or prostatic

TABLE 6.—*Simultaneous Determinations of the Urea Ratio and Urea Clearance Values in Patients with Bright's Disease*

No.	Patient	Whole Blood: Urea Nitrogen, Mg. per 100 Cc.	Whole Blood: Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Ratio	Urea Clearance, per Cent of Normal	Type of Bright's Disease*
1	Wal.	17.4	29.4	59.2	100.7	2
2	Ris.	14.4	29.8	48.3	88.1	2
3	Fri.	14.4	31.1	46.3	81.3	2
4	Ste.	16.2	33.1	48.9	65.1	2
5	Law.	12.1	25.7	47.1	64.0	5
6	Fin.	18.7	32.9	56.8	55.3	2
7	Riz.	14.6	27.0	54.1	53.6	2B
8	Kro.	26.9	50.4	53.4	49.6	5
9	Laz.	24.4	38.5	63.4	45.8	2B
10	Lev.	20.6	39.7	51.9	45.7	2
11	Fif.	14.9	26.2	56.9	45.5	1
12	Nus.	19.5	40.7	47.9	45.2	2A
13	Nus.	24.9	51.7	48.2	42.1	2A
14	Nus.	19.7	38.6	51.0	41.8	2A
15	Ell.	21.7	41.6	52.2	40.2	2A
16	Kro.	22.6	36.9	61.3	39.2	5
17	Lev.	22.8	41.9	54.4	36.2	2
18	Har.	20.6	35.1	58.7	36.1	5
19	Lev.	20.1	40.8	49.3	35.1	2
20	Gil.	27.9	41.1	67.9	34.4	2
21	Fad.	21.4	38.2	56.0	32.3	2
22	Fif.	18.2	33.8	53.9	32.0	1
23	Ell.	26.6	40.0	66.5	29.7	2A
24	Ell.	22.0	42.5	51.8	28.8	2A
25	Laz.	20.2	35.1	57.6	28.2	2B
26	Roe.	40.3	48.6	82.9	26.5	3
27	Ell.	18.5	38.9	47.6	26.2	2A
28	Ros.	33.4	56.6	59.0	26.0	2
29	Nat.	33.8	45.8	73.8	24.8	2
30	Gil.	31.8	57.2	55.6	24.2	2
31	Ros.	35.4	56.3	62.9	23.3	2
32	Ros.	35.3	55.1	64.1	23.3	2
33	Duf.	29.7	40.7	73.0	20.9	4
34	Leo.	43.2	71.4	60.5	18.8	2A
35	Ros.	44.0	56.3	78.1	18.7	2
36	Leo.	31.0	41.7	74.3	18.6	2A
37	Gee.	28.0	50.0	56.0	18.5	2A
38	Byr.	53.5	81.6	65.6	15.2	2
39	Ros.	51.4	72.7	70.7	14.5	2
40	Nat.	31.7	43.8	72.4	13.9	2
41	Gee.	46.0	70.6	65.2	12.8	2A
42	Gee.	74.1	117.6	63.0	12.5	2A
43	Sho.	58.8	76.9	76.5	11.6	2
44	Nus.	95.8	131.2	73.0	10.5	2A
45	Ell.	84.7	110.4	76.7	9.0	2A
46	Fis.	114.0	136.0	83.8	7.4	2C
47	Sag.	104.0	127.6	81.5	7.1	2C
48	Sag.	76.3	120.0	63.6	6.2	2C
49	Wit.	62.8	94.2	66.7	6.1	2
50	Gil.	167.1	222.2	75.2	4.8	2
51	Gol.	166.6	253.5	65.7	4.4	2C
52	Gos.	209.2	235.2	88.9	4.4	2C
53	Eck.	69.8	97.8	71.4	4.3	2C
54	Sab.	131.4	154.7	84.9	3.8	2
55	Sab.	128.6	147.0	87.5	3.0	2

* 1 indicates acute diffuse glomerular nephritis; 2, chronic diffuse glomerular nephritis, including that with (A) a nephrotic component, (B) an acute exacerbation of chronic diffuse glomerular nephritis, or (C) uremic manifestations; 3, focal embolic nephritis, and 4, amyloid nephrosis.

obstruction), the urea ratio was observed to be elevated when impairment of renal function was present. In patients with dyscrasias of the blood (agranulocytosis, polycythemia vera or leukemia), the urea ratio

was high. This may be due to an excessive destruction of the blood cells and a consequent increase in the urea within the blood stream. The renal insufficiency incidental to passive congestion was accompanied by an increase above the normal in the urea ratio. Patients with diseases of the liver showed a very low urea ratio. Nepveux and Hiernaux,[6] in 1927, called attention to this and ascribed it to the diminished activity of the liver in forming urea from the amino-acids in the blood.

COMMENT

Nepveux and Hiernaux,[6] in 1927, pointed out that Schondorff and Strauss in Germany and Widal and Rouchese, in 1906, in France were the first to study the "azotemic ratio," or, as we have termed it, the urea ratio. There has apparently been a lack of agreement on the significance of the ratio because of the widely different methods employed for the determination of the urea nitrogen and the total nonprotein nitrogen. Nepveux and Hiernaux noted that the urea ratio increases as the urea is retained in the blood in cases of Bright's disease. Mosenthal and Hiller,[1] in 1917, reported results identical with those given in this paper, except that their ratio was at a higher level because of the different chemical methods in vogue at that time for the determination of the total nonprotein nitrogen of the blood.

It is admitted that the concentrations of uric acid, creatinine and, at times, amino-acids and other forms of nitrogen rise in the blood as renal insufficiency develops; however, the urea nitrogen of the blood increases faster than the total amount of nitrogen contained in these substances, and, consequently, the urea ratio is elevated when renal function is impaired. An interesting point, and one that is of great importance in using the urea ratio as a test for renal function, is that it remains approximately constant no matter how the level of the nonprotein nitrogen of the blood is modified by diet or complications, such as vomiting and diarrhea. In other words, the urea ratio reflects the efficiency of the kidney, irrespective of the actual urea values of the blood.

The normal kidney is able to concentrate urea to a greater extent than any of the other nitrogenous derivatives of protein catabolism, with the exception of creatinine. For this reason, the partition of the nonprotein nitrogen in the blood and urine is not equal, the urea nitrogen, as has already been seen, constituting approximately 40 per cent of the total nonprotein nitrogen in normal laked blood (60 per cent in normal

6. Nepveux, F., and Hiernaux, A.: Valeur du rapport azotémique, Médecine **8**:757 (July) 1927.

unlaked blood [7]) and 80 per cent or more in the urine.[8] With the presence of a slight or moderate degree of renal insufficiency, the selective concentration of urea by the kidney is impaired. The result is that, even though no obvious retention of nitrogen in the blood takes place, there is a relative retention of nitrogen, and the ratio of urea nitrogen to the total nonprotein nitrogen is increased.

SUMMARY AND CONCLUSIONS

The urea ratio expressed as the percentage of urea nitrogen in the total nonprotein nitrogen in the blood, or $\frac{100 \times \text{urea nitrogen}}{\text{nonprotein nitrogen}}$ is a satisfactory index of renal efficiency. When the Folin-Wu filtrate (laked blood) is used for the determination both of the urea nitrogen and of the total nonprotein nitrogen in the blood, it is noted that the urea ratio varies with renal function as follows:

(*A*) with normal renal function, an index of 44 or less; (*B*) with maximal impairment of renal function, an index of 80 or higher; (*C*) with improvement in renal function, a drop in the ratio, and with progressive impairment of function, a rise in the ratio.

The determination of the urea ratio at intervals measures progressive changes in renal efficiency and affords a reliable index of renal function, regardless of the fluctuations of the total nonprotein nitrogen of the blood. Although the urea nitrogen or the total nonprotein nitrogen in the blood may be at a normal level, the urea ratio reveals renal insufficiency when it exists. This test may be carried out on one specimen of blood; it does not require prolonged observation of the patient or collection of urine. It furnishes a numerical index of the degree of impairment of renal function and is equally applicable to patients in private practice and to those in the hospitals.

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7. Folin, O., and Svedberg, A.: Diffusible Nonprotein Constituents of Blood and Their Distribution Between Plasma and Corpuscles, J. Biol. Chem. **88**:715, 1930.

8. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 272.

THERMAL STUDY OF VASOMOTOR LABILITY IN PREGNANCY

PRELIMINARY REPORT

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That vascular tension is an important factor in the mechanism of the toxemias of pregnancy was postulated many years ago. Cohnheim,[1] in 1880, seems to have been the first to express the view that albuminuria and anuria in eclampsia might be due to a spasm of the renal vessels. In 1918, Volhard [2] advanced the hypothesis that a generalized arterial spasm accounted for the hypertension, convulsions and renal symptoms in eclampsia. Heynemann [3] also assumed that a general arterial spasm produced the symptoms. Various attempts to demonstrate vascular spasm have been more or less successful. Hinselmann [4] (1924) noted the capillary changes in the finger-nail beds. He assumed that the capillary stasis and the dilatation were secondary to an arteriolar spasm. Subsequent observations of the nicking of retinal arteries and veins and the beading and the contractions of these vessels have indicated that the vascular spasm is probably general.

To our knowledge, no extensive studies of vascular tension in pregnancy have been made. Clinically, Adair [5] and deSnoo [6] have shown that essential hypertension is the characteristic feature of many cases of toxemia of pregnancy. Since vasomotor lability may be used as an index of vascular tension, we sought a simple method whereby the lability could be determined with reasonable accuracy. Kylin [7] (1926) emphasized the observations of Kaufman (1924) that patients

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1. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, A. Hirschwald, 1880.

2. Volhard, F.: Die doppelseitigen haematogenen Nierenerkrankungen (Brighl'sche Krankheit), Berlin, Julius Springer, 1918.

3. Heynemann, quoted by Fahr, in Hinselmann.[4]

4. Hinselmann, H.: Die Eklampsie, Bonn, F. Cohen, 1924.

5. Adair, F. L.: Analysis of a Series of Nonconvulsive Cases of Toxemias of Pregnancy, Am. J. Obst. & Gynec. **26**:530 (Oct.) 1933.

6. deSnoo, K.: Blood Pressure in the Pregnant, Monatschr. f. Geburtsh. u. Gynäk. **57**:235 (April) 1922.

7. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.

with hypertension showed a response to changes in external temperature that was different from that of normal persons. Stieglitz [8] called attention to the work of Hines and Brown,[9] who demonstrated that the vasomotor responses to the stimulus of cold water (4 or 5 C.) were apparently specific. These authors found that patients with primary hypertension and normal subjects with a family history of hypertension (prehypertension) gave higher responses to such a stimulus than did normal subjects with no family history of hypertension.

TECHNIC

The subject was placed in a comfortable chair or in a semireclining position in bed. All extraneous noises and distractions were reduced to a minimum. A preliminary period of rest lasted for from fifteen to thirty minutes. A blood pressure cuff was then applied to the arm, and the apparatus was raised to the cardiac level. An arm-band stethoscope was then adjusted to the cubital fossa, and the subject was permitted another short period of rest. From three to ten readings were taken at intervals of from five to ten minutes until a basal reading was obtained. The stimulus consisted of cold water, the temperature being approximately 1 C. This temperature was obtained by mixing chipped ice and water in a basin and immersing therein the extended hand of the arm bearing the blood pressure cuff until the ice-water reached the wrist. Blood pressure readings were taken immediately and then every thirty seconds for two minutes. After the test the hand was gently dried and another series of readings was taken at intervals of thirty seconds in order to determine the length of time required for the blood pressure to approach the basal level.

OBSERVATIONS

One hundred and ninety women were studied. They were divided into two groups—the pregnant and the nonpregnant. Whenever possible, an attempt was made to obtain an accurate family history of hypertension. The pregnant patients were grouped as follows: normal, preeclamptic, eclamptic and having chronic nephritis. The preeclamptic group was composed of primiparas who had edema, hypertension and albuminuria and usually other symptoms, such as diplopia, dizziness, headaches, oliguria, etc. The onset of the toxemia occurred in the last six or eight weeks of pregnancy. The eclamptic group differed in that the patients, in addition, had convulsions and/or coma. The group with chronic nephritis was composed of the remainder of the patients and included those with primary hypertension, chronic glomerulonephritis and a recurrence of toxemia. The observations were carried out at prolonged intervals, and as many as eight tests were made on some patients.

8. Stieglitz, E. J.: Personal communication.

9. Hines, E. A., Jr., and Brown, G. E.: Standard Stimulus for Measuring Vasomotor Reactions: Its Application in the Study of Hypertension, Proc. Staff Meet., Mayo Clin. **7**:332 (June 8) 1932.

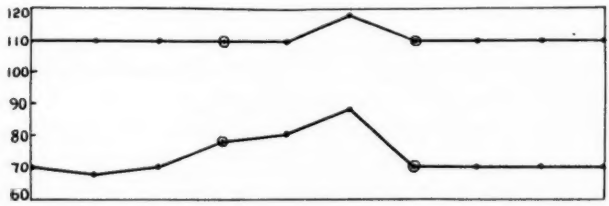

Fig. 1.—Typical graph of the blood pressure of nonpregnant women without a family history of hypertension.

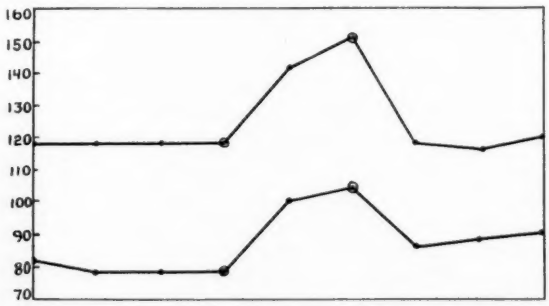

Fig. 2.—Typical graph of the blood pressure of nonpregnant women with a family history of hypertension.

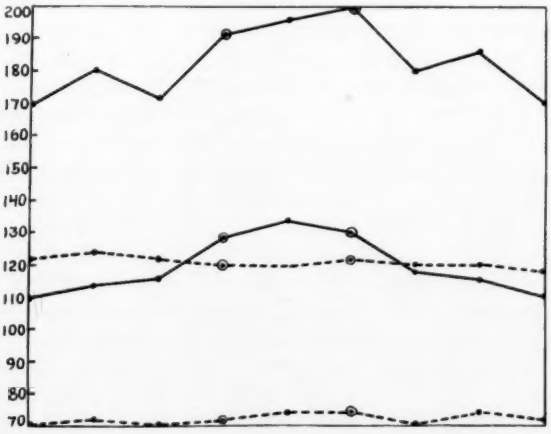

Fig. 3.—Typical graph of the blood pressure of a preeclamptic patient in the antepartum and postpartum periods. In figures 3 to 5 the solid lines represent the readings before delivery; the dotted lines, the readings after delivery.

In a group of twenty-eight nonpregnant subjects with a family history of hypertension, the mean rise in blood pressure was 35.07 mm. of mercury systolic and 34.5 mm. diastolic. In forty-two nonpregnant

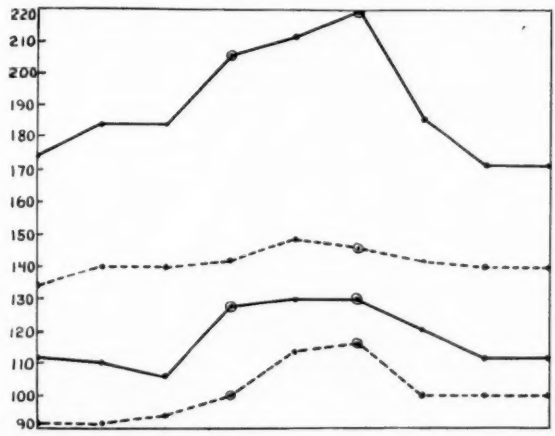

Fig. 4.—Typical graph of the blood pressure of an eclamptic patient in the antepartum and postpartum periods.

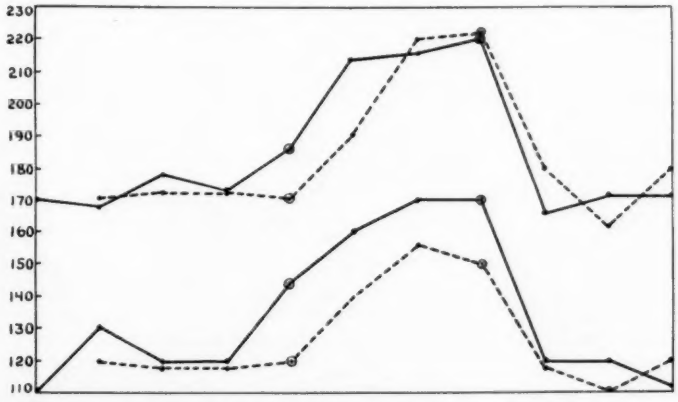

Fig. 5.—Typical graph of the blood pressure of a patient with clinical nephritis in the antepartum and postpartum periods.

women giving no definite family history of hypertension the mean rise was 18.76 mm. systolic and 23.3 mm. diastolic. Six patients with essential hypertension showed an increase of 36 mm. systolic and 36 mm. diastolic. In another group of six patients with symptoms of

vasomotor instability and no family history of hypertension, the average increase was 37 mm. systolic and 35.3 mm. diastolic.

In eighteen normal pregnant women without a family history of hypertension the mean antepartum rise was 19.56 mm. systolic and 19.8 mm. diastolic, and the postpartum rise was 15.11 mm. systolic and 22 mm. diastolic. In contrast, in thirteen normal pregnant women with a family history of hypertension the mean antepartum increase was

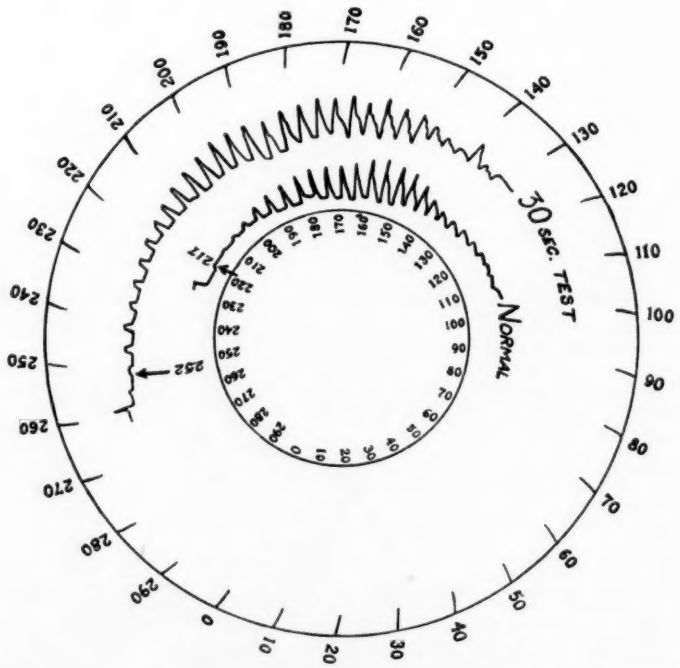

Fig. 6.—A graph obtained with a Tycos self-recording sphygmomanometer. *Normal* shows the basal reading before the application of ice-water. The adjacent graph was obtained thirty seconds after immersion of the hand in ice-water.

35.54 mm. systolic and 26.1 mm. diastolic; the postpartum rise was 39 mm. systolic and 34 mm. diastolic.

In the preeclamptic group the mean antepartum increase was 26.06 mm. systolic and 23.6 mm. diastolic, as compared with the postpartum rise of 26 mm. systolic and 15.3 mm. diastolic.

Five patients with eclampsia showed a mean antepartum increase of 26 mm. systolic and 16.7 mm. diastolic.

In thirty-three patients who were designated clinically as having chronic nephritis, the mean antepartum rise was 51.88 mm. systolic and 37.5 mm. diastolic, as compared to the postpartum rise of 51 mm. systolic and 35.8 diastolic.

TABLE 1.—*Fluctuations in the Systolic Blood Pressure Caused by a Standard Stimulus* *

Increase in Systolic Pressure, Mm. Mercury	Normal Nonpregnant Patients		Pregnant Patients			
			Family History of Hypertension		No History of Hypertension	
	Family History of Hypertension	No History of Hypertension	Ante Partum	Post Partum	Ante Partum	Post Partum
0 to 9	..	4	..	..	5	2
10 to 19	1	15	..	..	3	4
20 to 29	5	20	4	..	6	3
30 to 39	15	3	6	3	3	..
40 to 49	4	..	1	3	1	..
50 to 59	3	..	1	..	..	..
60 to 69	..	..	1	..	..	..
Total number of patients	28	42	13	6	18	9
Mean increase in systolic pressure	35.07	18.76	35.54	39.0	19.56	15.11
S. D.	9.43	8.97	11.74	7.07	12.92	7.46
P. E.	1.2	0.93	2.2	1.95	2.05	1.68

* In this table one notes a significant difference in the response between those subjects who gave a family history of hypertension and those who did not, irrespective of the presence of pregnancy. In tables 1 and 2 S. D. indicates standard deviation; P. E., probable error.

TABLE 2.—*Fluctuations in the Systolic Blood Pressure in Toxemic Patients with Hypertension* *

Increase in Systolic Pressure, Mm. Mercury	Nephritic Toxemia		Preeclampsia		Eclampsia	
	Ante Partum	Post Partum	Ante Partum	Post Partum	Ante Partum	Post Partum
0 to 9	..	..	..	1	1	..
10 to 19	..	..	7	8	1	2
20 to 29	..	..	16	17	1	2
30 to 39	4	6	9	11	..	..
40 to 49	14	1	1	2	2	1
50 to 59	6	8	1	1	..	..
60 to 69	5	4	..	..	..	..
70 to 79	2	..	..	..	..	..
80 to 89	2	1	..	..	..	..
Total number of patients	33	20	34	40	5	5
Mean increase in systolic pressure	51.88	51	26.06	26	26.0	
S. D.	25.21	13.78	9.22	10	16.13	
P. E.	2.84	0.84	1.07	1.07	4.86	

* This table represents a comparative study of the responses from a group of patients with toxemia and hypertension in pregnancy. Note the marked responses in the patients with nephritic toxemia, as compared with the preeclamptic and eclamptic patients.

In table 1, we present the biometric analysis of the data on the normal nonpregnant and the normal pregnant women used as controls, illustrating the variations and the means of the fluctuations in the systolic blood pressure caused by the standard stimulus. It is interesting to note that when the patients gave a family history of hypertension,

the mean increases were the same, and when the family history was negative, the mean increases again were the same. The differences, however, are significant.

In table 2 is similarly presented the biometric analysis of the data on the toxemic patients, giving the variations and the means for this group. The mean rise for the group with chronic nephritis is double that for the preeclamptic and the eclamptic group. The increase in the

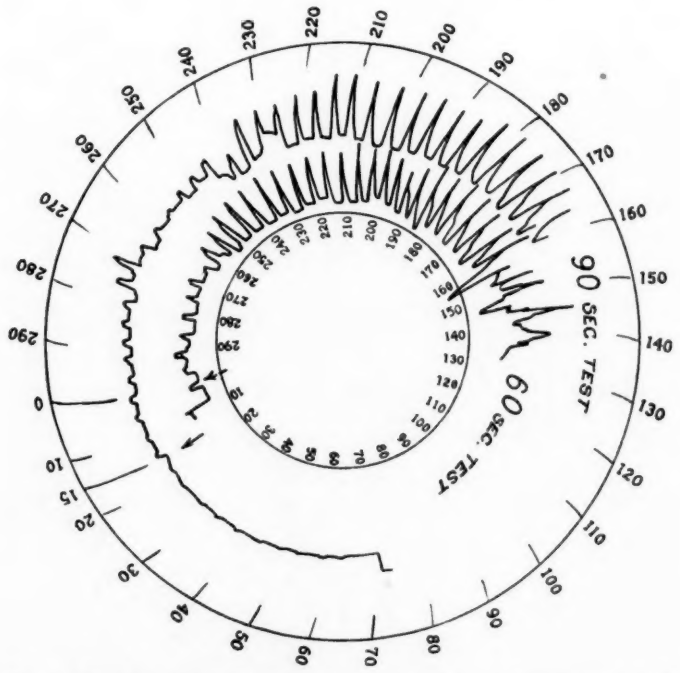

Fig. 7.—Graph obtained with a Tycos self-recording sphygmomanometer, illustrating the responses obtained sixty seconds and ninety seconds, respectively, after immersion of the hand in ice-water.

nephritic group is significant. The increase in the preeclamptic and the eclamptic patients is also significant if compared with the data for the pregnant patients who gave no history of hypertension.

MECHANISM OF RESPONSE

It appears that the response is purely that of a pain reflex, as suggested by Hines and Brown. The promptness of the reaction excludes

chemical or hormonal factors. If a tourniquet is applied to the arm that is immersed in ice-water and blood pressure readings are taken on the opposite arm, there is no significant variation in the response. The pain reflex is best illustrated when the test is made during labor. The response obtained with ice-water between labor pains is equivalent to the systolic rise recorded during the pains without the application of the ice-water. Furthermore, the response during anesthesia is inhibited.

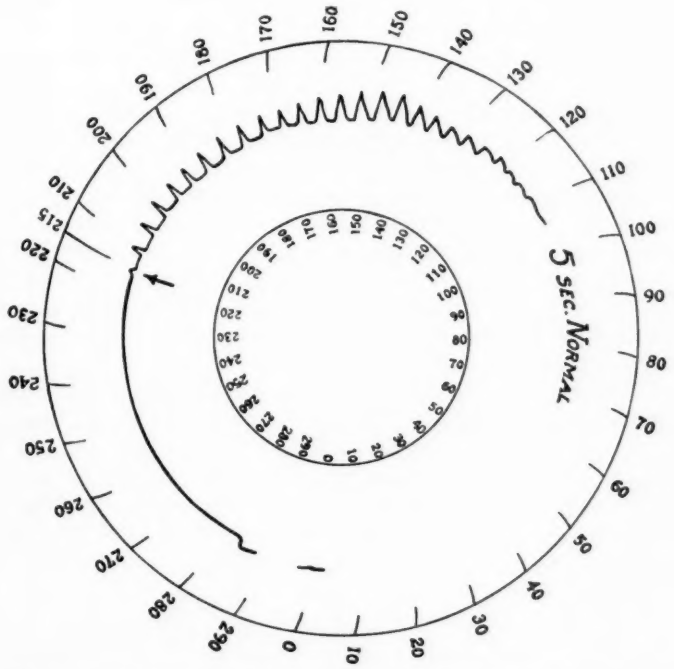

Fig. 8.—Graph obtained with a Tycos self-recording sphygmomanometer, illustrating the rapid return to normal five seconds after the hand was removed from the ice-water.

COMMENT

It is interesting to note that the patients with chronic nephritis exhibited marked vasomotor lability. Five of the patients in this group manifested severe reactions during the test or shortly afterward. The reactions of these five patients were as follows:

The first patient in this group had blurred vision and developed convulsions one hour after the completion of the test.

The second patient complained of intolerable epigastric pain immediately after the test, and within one hour had hematuria and casts in the urine, followed by anuria and collapse of the vasomotor type.

The third patient collapsed during the height of the test.

The fourth patient had severe epigastric pain, blindness, nausea and emesis during the test.

The fifth patient had an increase in blood pressure of 60 mm. during the test, and the blood pressure remained elevated for seven days, until she was discharged.

The close association of these responses with the test strongly suggests that a vascular disturbance was the cause.

A careful analysis was made in this group to determine whether or not there was a correlation between the marked vasomotor response and the renal impairment. The diagnosis of chronic nephritis, as previously stated, was established chiefly from a clinical point of view, with the following criteria in mind: (1) elderly multiparas; (2) a history of previous toxemia of pregnancy; (3) symptoms and findings appearing in the first or second trimester; (4) a history of scarlet fever during childhood with prolonged convalescence; (5) findings of hypertension, albuminuria or edema, and (6) symptoms of headaches, dizziness, nausea, emesis or blurred vision.

Comprehensive laboratory analyses were made in these cases, particular attention being given to the nonprotein nitrogen, blood urea nitrogen, urea clearance, output of urine per hour, specific gravity and sediment. The results indicated that all of these patients had a hypertension at that time or had had it at some previous period, and that there was either slight or marked evidence of a renal pathologic process in all of them. However, only a few could be classified as having chronic glomerulonephritis.

Presumably, then, the clinical phenomena which these patients manifested were attributable to alterations in the vascular system. Whether these alterations were initiated by toxic, neurogenic, chemical or hormonal influences was not clear, but they did appear to be characterized by a marked vasomotor lability which strongly identifies the mechanism as being a vasospasm.

If it is assumed that a general arteriolar spasm does occur, there is a possible explanation for the urinary findings: hypertension, edema and eclamptic convulsions.

The influence of vasospasm and vasodilatation on urinary output has been emphasized by many of the early investigators. Bernard [10]

10. Bernard, C.: Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme, Paris, J. B. Baillière, 1859.

and Eckhard[11] sectioned the spinal cord in the cervical portion in rabbits and in dogs. The vascular tension was reduced to 40 mm. and urination ceased. Stimulation of the brain stem and spinal cord caused renal vasoconstriction with diminished renal circulation. Ustimovitsch[12] sectioned the renal nerves in dogs, producing vasodilatation and an increased urinary flow. Thus, there is a definite relationship between vascular tension and urinary output.

Intense spasm in the renal vessels may lead to oliguria and even to anuria and, if unduly prolonged, to destruction of the glomeruli and the tubules. This renal anemia may account for alterations in capillary permeability with the consequent appearance of blood proteins (albumin) in the urine. With the precipitation of albuminous material in the tubules, casts may be formed. It is also possible that the occurrence of edema and convúlsions is closely associated with the vascular alterations. It is important to note that this group of patients continued to show marked vasomotor lability for months after delivery. At repeated late postpartum visits one could observe the persistence of hypertension in over 50 per cent of these patients.

The relatively small increases in systolic pressure in the eclamptic and preeclamptic groups afford an opportunity for speculation and conjecture. Apparently in these patients the vascular spasm is at its maximum or there is a diminished response to pain stimuli. This has been demonstrated by Spiegler and Schol,[13] who found that eclamptic patients required a greater cathodal closing current to elicit a contraction than did normal pregnant women. Evidently in chronic nephritis the vascular system is more labile and the nervous system more irritable, or there may be some loss of elasticity of the walls of the vessels, which results in a greater response to stimuli.

The number of observations is too small and the period over which the patients have been followed is too short to permit the drawing of any definite conclusions, but the following statements seem justifiable:

A larger series of patients and a more accurate method for determining vascular lability may demonstrate conclusively that the toxemia of pregnancy is closely associated with vascular spasm.

The test may be of value in determining permanent renal vascular damage after delivery.

The test may enable one to detect early in pregnancy those patients in whom toxemia is likely to develop.

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11. Eckhard: Beitr. z. Anat. u. Physiol. **4**:155, 1869.

12. Ustimovitsch: Ber. ü. d. Verhandl. d. k. sächs. Gesellsch. d. Wissensch. z. Leipzig, Math.-phys. Cl. **22**:430, 1870.

13. Spiegler, R., and Schol, W.: Die galvanische Nerven-Muskelerregbarkeit in der Schwangerschaft und bei Toxikosen, Arch. f. Gynäk. **141**:651, 1930.

The test may also enable one to determine early in pregnancy whether or not a patient with a history of previous toxemia is likely to have a recurrence.

SUMMARY

One hundred and ninety patients were subjected to a standard ice-water stimulus, and blood pressure readings were obtained at definite intervals during the test.

Nonpregnant subjects with a family history of hypertension gave more marked responses to the test than nonpregnant subjects without such a family history. Similar results were obtained in a group of pregnant subjects.

In a group of patients with toxemia of pregnancy no uniform results were noted during the preeclamptic period or during the eclampsia.

Those patients in whose cases a diagnosis of chronic nephritis had been made gave marked responses before, as well as after, delivery. Subsequent laboratory analyses indicated that all of these patients had hypertension at that time or had had it at an earlier period and that there was either slight or marked evidence of a renal pathologic process in many of them. Only a few, however, could be classified as having chronic glomerulonephritis.

In five patients belonging to the chronic nephritic group untoward reactions were obtained that identified the condition as a vascular disturbance.

Vascular tension as an important factor in the toxemias of pregnancy is emphasized and discussed.

The possibilities of the test as an aid in the diagnosis and prognosis of vascular disturbances during pregnancy are considered.

ESTROGENIC, LUTEAL AND GONADOTROPIC HORMONES IN HEMOPHILIA

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In another communication [1] observations were reported on seven patients with hemophilia in whom no demonstrable improvement in the coagulation of the blood or in the clinical state resulted from the oral and parenteral administration of various ovarian and estrogenic substances.

The failure to enhance the coagulability of the blood in hemophilia by the administration of an estrogenic substance has been noted by Blaylock,[2] who observed a slight increase in the coagulation time of the blood of his patient with hemophilia one week after starting daily subcutaneous injections of an "ovarian preparation obtained from the fetal fluid of cattle." Brown and Albright [3] similarly observed no beneficial effect in one patient with hemophilia who was given injections of large amounts of estrogenic substance over a period of three days. More recently, Brem and Leopold [4] have reported negative observations on the coagulation time and clinical state of a patient with hemophilia given intramuscular injections of extract of whole ovary daily for three weeks, followed by the daily intramuscular injection of estrogenic substance for two weeks.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard University Medical School (Dr. Chew and Dr. Stetson), with the cooperation of the Fearing Research Laboratory of the Free Hospital for Women, Brookline, Mass. (Drs. Smith).

1. Stetson, R. P.; Forkner, C. E.; Chew, W. B., and Rich, M. L.: The Negative Effect of Prolonged Administration of Ovarian Substance in Hemophilia, J. A. M. A. **102**:1122 (April 7) 1934.

2. Blaylock, A.: Amputation of Arm of Patient with Hemophilia, J. A. M. A. **99**:1777 (Nov. 19) 1932.

3. Brown, R. L., and Albright, F.: Estrin Therapy in a Case of Hemophilia, New England J. M. **209**:630 (Sept. 28) 1933.

4. Brem, J., and Leopold, J. S.: Ovarian Therapy: Relationship of the Female Sex Hormone to Hemophilia, J. A. M. A. **102**:200 (Jan. 23) 1934.

These results are at variance with those of Birch [5] and others,[6] who have reported a marked diminution in the coagulation time and an improvement in the clinical condition of patients with hemophilia under treatment with ovarian substances and various preparations of so-called "female sex hormones."

The work of Hynek,[7] in 1923, suggested that a substance contained in the corpus luteum might influence the coagulation time of the blood of persons with hemophilia. He reported the normal clotting of blood of patients with hemophilia following the injection of a preparation of corpus luteum. Birch [5b] stated that she had obtained good results from the administration of lutein preparations. However, Neihans,[8] in 1930, observed an improvement in one patient with hemophilia following the transplantation of an ovary devoid of corpus luteum, whereas the transplantation of an ovary containing corpus luteum into another patient with hemophilia resulted in no improvement.

The limitation of hemophilic manifestations to the male sex provides speculative interest in the theory that some substance peculiar to female physiology inhibits the appearance of these manifestations in the female, through whom the condition is transmitted. This theory was strengthened materially by Birch,[9] who failed to detect estrogenic substance in the urine of seven males with hemophilia or in two "transmitters," while extracts from the urine of normal males consistently induced estrus in rats. Brown and Albright,[3] on the contrary, found more than 40 rat units of this substance in a twenty-four hour specimen of urine of their patient with hemophilia before treatment, while there were more than 480 rat units in a twenty-four hour specimen of his urine after the intensive administration of estrogenic substance. No determinations of the estrogenic factor of the blood were reported in this case, but it seems reasonable to agree with the conclusions of these investigators that "the presence of estrin [estrogenic substance] in the

5. Birch, C. L.: (*a*) Hemophilia, Proc. Soc. Exper. Biol. & Med. **28**:752 (April) 1931; (*b*) Hemophilia, J. A. M. A. **99**:1566 (Nov. 5) 1932.

6. Foord, A. G., and Dysart, B. R.: Treatment of Hemophilia by an Ovarian Extract by Birch's Method, J. A. M. A. **98**:1444 (April 23) 1932. Kimm, H. T., and Van Allen, C. M.: Hemophilia: Prevention and Treatment of Bleeding with Ovarian Extract, J. A. M. A. **99**:991 (Sept. 17) 1932. White, C. E.: Treatment of Hemophilia with Theelin, J. Oklahoma M. A. **25**:304 (July) 1932. Hirst, J. C.: The Influence of Female Sex Hormones upon Blood Coagulation of the Newborn, Am. J. Obst. & Gynec. **26**:217 (Aug.) 1933. Spoto, J. S.: Treatment of Hemophilia with Ovarian Extract, J. Florida M. A. **20**:9 (July) 1933.

7. Hynek, K.: Nouvelles considérations sur l'hémophilie, Ann. de méd. **14**:122 (Aug.) 1923.

8. Neihans, P.: Treatment of Hemophilia, Schweiz. med. Wchnschr. **60**:18 (Jan. 4) 1930.

9. Birch, C. L.: Hemophilia and the Female Sex Hormone, J. A. M. A. **97**:244 (July 25) 1931.

blood stream, presumably in amounts far greater than found in normal women as judged by the urinary excretions did not in itself alter the coagulation time in a case of hemophilia." Brem and Leopold [9] were unable to demonstrate estrogenic substance in the urine of normal males, and in the urine of two patients with hemophilia who had not received treatment or in the urine of one patient with hemophilia during treatment with intramuscular injections of ovarian extract or of ovarian follicular hormone. The difference in technic employed by the various investigators and the little understood nature of the substances tested help to explain the conflicting results obtained.

It is beyond the scope of this paper to present in detail the facts and theories about the various factors designated as "female sex hormones." It is pertinent, however, to describe briefly the differential features of these hormones so far as they concern our problem.

The estrus-inducing substance of the ovary is produced by the graafian follicle, the corpus luteum and the placenta. Its effect is exerted primarily on the lower genital organs of the female, producing growth and vascularization of the uterus and growth and cornification of the vaginal epithelium in animals. It also promotes the development of secondary sex characters, but its administration is without effect on the ovaries except when given in large doses, when it may depress follicular growth, apparently through an inhibitory action on the anterior lobe of the hypophysis. The usually employed measure of potency of estrus-inducing substances is the rat unit of Allen and Doisy, which is equivalent to 5 mouse units.

In normal women who menstruate regularly, the quantity of estrogenic principle in the blood gradually increases during the intermenstrual period to a maximum concentration during the second half of the cycle. Just before and with menstruation the concentration of estrogenic substance in the blood falls rapidly, but if pregnancy occurs, the concentration rises slightly during the first three or four months and then rises to a high level by the time of parturition. Urine from pregnant women and amniotic fluid provide two abundant sources of estrogenic substance for commercial use.

An estrogenic hormone is recoverable from the urine and blood of normal males which has a physical and biologic similarity to that found in the female. From a consideration of the available evidence, Mazer and Goldstein [10] concluded that the estrogenic factor found in the male and that found in the female "produce similar reactions in the lower genital tract of the female castrated rodent; that the male sex

10. Mazer, C., and Goldstein, L.: Clinical Endocrinology of the Female, Philadelphia, W. B. Saunders Company, 1933.

hormone prevents the appearance of castration atrophy in the seminal vesicles and prostate; that the action of estrin upon the accessory organs of the male animal is still debatable."

The corpus luteum produces, in addition to the estrogenic substance, the lutein hormone, progestin, the demonstrated actions of which in adult female animals are: to sensitize the endometrium and prepare it for the implantation of the fertilized ovum after the estrogenic factor has exerted its vascularizing effect; to promote the excretion of estrogenic substance and to inhibit ovulation and estrus. It also has an inhibitory effect on uterine contractions. Progestin is relatively unstable and is not available for ordinary therapeutic use in any considerable amount. Its potency is expressed in rabbit units. As yet, this hormone has not been recovered from the blood or the urine.

The third sex hormone with which we are concerned is one the effects of which have been identified in part with those of the gonad-stimulating hormones of the anterior lobe of the pituitary gland, the anterior pituitary-like gonadotropic hormone. This hormone is non-specific for sex, but in the female two distinct actions have been demonstrated. The action on the ovaries of test animals may be to stimulate the maturation of follicles and hence the production of estrogenic substance (the so-called prolan A, or rho I effect) or to precipitate hemorrhages into the follicles and cause a rapid formation of corpus luteum with its consequent production of progestin (the so-called prolan B, rho II, or the luteinizing effect). It is debatable whether these effects are dependent on the production of two distinct hormones by the anterior lobe of the pituitary gland or whether the influence is quantitative. The first effect can be evoked by the administration of small amounts of anterior pituitary-like gonadotropic hormone, whereas larger amounts serve to produce luteinization. In the male, the anterior pituitary-like gonadotropic hormone stimulates the testes to produce the testis hormone, and possibly has other effects. The gonadotropic preparations are standardized in terms of the rat unit.

Traces of the gonadotropic factor are constantly present in the blood of every adult, although not always in sufficient quantity to be demonstrable by ordinary methods. During pregnancy the amount is greatly increased to a maximum at the fourth or fifth month, after which there occurs a gradual diminution until term. The large quantity of this hormone recovered in the urine of pregnant women provides most of the supply used in commercial preparations. There is considerable evidence that the hormone found in the urine of pregnant women is not hypophyseal, but rather a placental product with gonadotropic activity.

In this communication we are reporting observations on the coagulation time of the blood and on the gonadotropic principle in the blood

and the gonad-stimulating and estrogenic substances in the urine of two patients with hemophilia during control periods when no particular therapy was employed and while receiving the various preparations to be listed in the quantities indicated in charts 1 to 3. Two other patients were observed while receiving no therapy and after one subcutaneous injection of the anterior pituitary-like gonadotropic hormone.

Each of the patients since infancy or early childhood had experienced characteristic episodes of hemophilia, including hemarthroses. One or more members of the family of each was similarly affected. During control periods and when receiving therapy, each of the group occasionally showed mild manifestations of bleeding. In none were there any significant abnormalities of the formed elements of the blood other than a mild degree of hypochromic anemia. All had received large doses of ovarian substance without benefit, as reported previously.[1]

MATERIALS

The preparations used in carrying out the tests were:

1. Follutein, the anterior pituitary-like gonad-stimulating hormone obtained from the urine of pregnant women, which stimulates the ovaries of rats, mice and rabbits to the maturation of follicles and the luteinization, assayed by the manufacturer to contain 250 rat units per cubic centimeter.

2. Luteo-hormone, a commercial extract of corpus luteum, assayed by the manufacturer to contain 0.04 rabbit unit of "lutein hormone" per cubic centimeter.

3. Luteo-hormon, the same as that described in 3, but assayed to contain 10 rabbit units of "lutein hormone" per cubic centimeter.

4. Theelol, estrogenic substance for oral administration, assayed by the manufacturer to contain 500 rat units per capsule.

5. Theelin, an estrogenic substance for subcutaneous or intramuscular administration, assayed by the manufacturer to contain 50 rat units per cubic centimeter.

In addition, one patient (patient 5) received small doses of roentgen rays over the pituitary region.

The theoretical considerations which prompted the trial of these preparations of hormones should be mentioned. The use of estrogenic substance was based on Birch's[9] observations that there was no estrogenic substance in the urine of hemophilic patients. However, contrary to her observations, the patients reported on here tended to have excessive rather than subnormal amounts of estrogenic substance in the urine. The corpus luteum hormone, progestin, has been found to enhance the excretion of estrogenic substance in rabbits and in human beings.[11] Assuming that the usually excessive excretion of the estrogenic factor by hemophilic patients signified a high level of this substance

11. Smith, G. V., and Smith, O. W.: Studies on the Urinary Excretion of Estrin, with Especial Reference to the Effect of the Luteinizing Hormone and Progestin, Am. J. Physiol. **98**:578 (Nov.) 1931.

in their blood stream, it was thought that the administration of preparations of corpus luteum might be beneficial by promoting such excretion.

Excessive menstrual flow in women has often been found to be associated with the appearance of the follicle-stimulating principle in the blood and urine.[12] Since this principle was present in demonstrable amounts in the blood and urine of some of our hemophilic patients and since excessive menstrual flow in women is benefited in many instances by the administration of the gonadotropic hormone found in the urine of pregnant women, it was considered logical to give an anterior pituitary-like gonadotropic hormone a trial.

METHODS

The coagulation time of the venous blood was determined by the method of Lee and White, modified as described in a previous communication.[1] Only the time of complete coagulation of the blood is recorded in the present study. For the sake of simplicity, the time of surface coagulation and the coagulation time of the capillary blood measured in a capillary tube, which were determined simultaneously, are not reported. In general they paralleled the complete coagulation time, with perhaps less marked variation.

For the determination of estrogenic substance, a forty-eight hour specimen of urine was collected, acidified with dilute hydrochloric acid and extracted for ten hours with chloroform in a modification of the apparatus for continuous extraction by means of chloroform described by Frank.[13] The extraction of urine of known potency by this method has shown that not all of the estrogenic substance is recovered. A comparison of our figures on the urine of normal males with some of the figures reported in the literature indicates that other methods of extraction may be more efficient (we have experimented subsequently with other methods and have found that, although none of them give a quantitative recovery, the Kurzrok method [that used by Brown and Albright [3]] yields more than other methods so far tried). However, since the urine of both hemophilic and normal males was extracted by the same process, the results reported are comparable.

[NOTE.—Since this work was done we have discovered that the boiling of urine with 15 per cent hydrochloric acid often results in as much as a twenty-fold increase in estrogenic potency. A study of the existing methods of extracting the estrogenic substance of urine has revealed that none of them can be counted on to give a complete recovery of the amount actually shown to be present unless the specimens are first boiled with acid. We have also found that the proportion of the "total" estrogenic substance recoverable from untreated specimens is not constant, but depends on unknown and variable urinary factors, so that whatever the extractive agent the results so acquired may not even be considered comparable and are of questionable quantitative significance.—G. V. and O. W. Smith.]

In the early stages of the investigation the residue left after the chloroform had been evaporated was taken up in a physiologic solution of sodium chloride to be tested on spayed female rats. It was found later that with the use of olive oil for this purpose somewhat larger amounts of estrogenic substance were demonstrated.

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12. Smith, G. V., and Rock, J.: Dysfunctional Uterine Bleeding, Surg., Gynec. & Obst. **57**:100 (July) 1933.

13. Frank, R. T.: Rôle of the Female Sex Hormone, J. A. M. A. **97**:1852 (Dec. 19) 1931.

There were normal controls for both methods (chart 3). Not all the chloroform was distilled off before the addition of the physiologic solution of sodium chloride or olive oil, the last of the evaporation being performed in a small receptacle on the steam bath. The material was injected first into two rats in amounts testing for 4 rat units. If neither rat showed estrous smears (a negative reaction) the material was tested for 2 rat units, which exhausted the material. With specimens of urine containing more than 4 rat units it was possible to use from four to eight rats for the final assay.

In testing for the gonadotropic factor, from 5 to 10 cc. of blood serum, or the amount of urine equivalent to 10 mg. of creatinine, was extracted by the Aschheim-Zondek method; i. e., the material was shaken with five volumes of a 95 per cent solution of alcohol, was then allowed to stand overnight and was centrifugated. The precipitate was washed with ether and taken up in 6 cc. of physiologic solution of sodium chloride for injection into immature female rats. Urine or blood serum from normal males in these amounts has no effect on the ovaries of immature rats. Any grossly apparent enlargement of the ovaries or uterus was considered a positive reaction.

RESULTS

Patient 1,[14] a 27 year old Jewish man, the brother of the patient in case 6, was completely ambulatory during the course of the observations recorded in chart 1.

Period 1 shows the fluctuation of the coagulation time of his blood during eight months when no specific therapy was given other than one subcutaneous injection of follutein. This period demonstrates the marked fluctuations of the coagulation time which occurs spontaneously in untreated patients with hemophilia and which must be recognized when one attempts to evaluate the effect of therapy. The increased coagulation time during the winter suggests a seasonal variation, which we have observed in other patients with hemophilia.

On the seventh day of period 3 the coagulation time was increased to eight hours and fifteen minutes, and there developed a large hematoma of the shoulder. On the last day of the period the coagulation time had diminished, but the patient had slight bleeding from his gums. No treatment was given during the ensuing twenty-six days (period 4), during which the coagulation time was comparable to that recorded in the latter part of period 1.

Patient 5, a 28 year old man of German extraction, was in the hospital almost continuously for two years. The therapy he received and the observations on the coagulation time of his blood are recorded in chart 2.

During periods 2, 3 and 4 the average coagulation time was longer than that during the preceding control period. On the last day of period 3 a small hematoma developed on the dorsum of one hand without known trauma, and on the tenth day of period 4 he experienced slight bleeding

14. The numbers correspond to those assigned the patients in our previous report.[1]

around a tooth. The increase in the coagulation time during periods 2, 3 and 4 is striking, but not sufficient to be of itself significant, as it is not beyond the range of spontaneous fluctuation which has been encountered in this patient and in others with hemophilia (chart 1, period 1). Eight months before this series of observations, he had received three subcutaneous injections of 200 rat units each and three injections of 300 rat units each of a different preparation of an anterior pituitary-like gonadotropic hormone ("Antuitrin S") over a seven day period. Before treatment the coagulation time was four hours and five minutes, on the sixth day it had diminished to one hour and ten minutes,

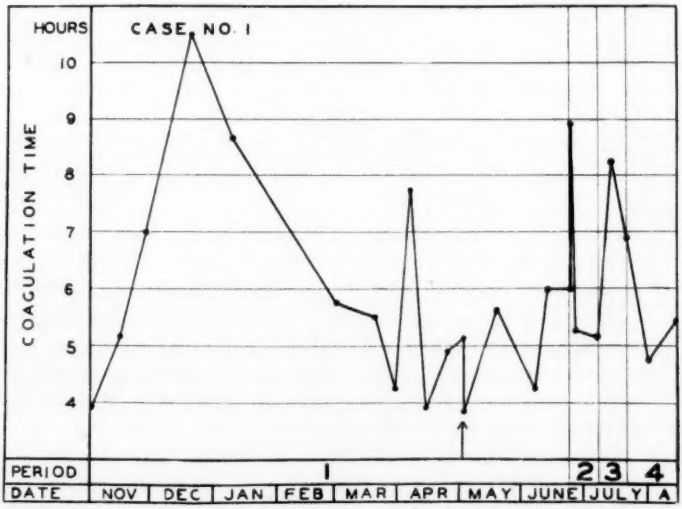

Chart 1 (case 1).—A record of the coagulation time of the venous blood during the indicated periods. In period 1 (eight months) there was no therapy other than one subcutaneous injection of 250 rat units of follutein on May 3 (shown by the arrow). In period 2 (eleven days) a single intramuscular injection of 4 rabbit units of luteo-hormon was given followed by ten daily intramuscular injections of 0.04 rabbit unit of luteo-hormon. In period 3 (fourteen days) 19 rabbit units of luteo-hormon was given in six intramuscular injections. In period 4 (twenty-six days) there was no therapy.

and five days after treatment was discontinued it was two hours and fifteen minutes. The treatment is comparable to that given in period 2, but the behavior of the coagulation time of the blood in the two periods is absolutely contrary.

The three weekly exposures to the roentgen rays given in period 9 were in accord with the technic and dosage described by Mazer and Goldstein,[10] by which they claimed to stimulate the production of the

gonadotropic principle of the anterior pituitary gland in persons with gynecological disturbances (127 kilovolts, 5 milliamperes, filtered with 5 mm. of aluminum at a target distance of 14 inches for five minutes over the pituitary region). The increase in the coagulation time following the initial drop after the first treatment might be construed as evidence of a harmful effect of the treatments, which were continued through the subsequent control period. It is certain that the treatment failed to enhance the coagulability of the blood.

The administration of estrogenic substance (theelin) subcutaneously was carried on during the fifty-one days of periods 11 and 12. The curve recording the coagulation time during these periods shows a marked downward course, covering a range of nearly four hours. However, the first determination in control period 13 was made only two days after the last injection of theelin and is at essentially the same level as before treatment.

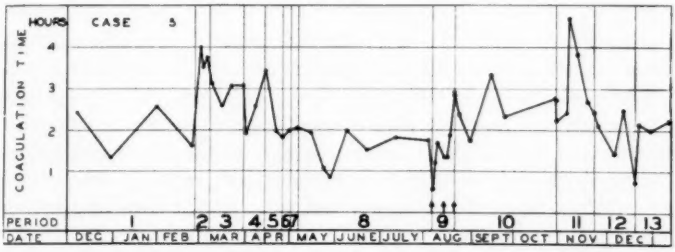

Chart 2 (case 5).—A record of the coagulation time of the venous blood during the indicated periods. In period 1 (eighty-five days) there was no therapy. In period 2 (nine days) 250 rat units of follutein was given subcutaneously daily. In period 3 (twenty days) 125 rat units of follutein was given subcutaneously daily. In period 4 (fifteen days) 125 rat units of follutein was given subcutaneously, and 1,500 rat units of theelol was given orally, daily. In period 5 (twelve days) 125 rat units of follutein was given subcutaneously, and 0.04 rabbit unit of luteo-hormon was given intramuscularly, daily. In period 6 (seven days) 125 rat units of follutein was given subcutaneously, and 0.08 rabbit unit of luteo-hormon was given intramuscularly, daily. In period 7 (five days) 250 rat units of follutein was given subcutaneously, and 0.08 rabbit unit of luteo-hormon was given intramuscularly, daily. In period 8 (eighty-eight days) there was no therapy. In period 9 (fifteen days) there were three roentgen ray exposures over the pituitary region. In period 10 (sixty-nine days) there was no therapy. In period 11 (twenty-five days) 50 rat units of theelin was given subcutaneously every second day. In period 12 (twenty-six days) 50 rat units of theelin was given subcutaneously twice a week. In period 13 (thirty days) there was no therapy.

Formerly [1] we were unable to demonstrate a change in the coagulation time resulting from the daily subcutaneous injection of 50 rat units of estrogenic substance. The injections as carried out in periods 11 and

12 were undertaken because of the statement of Wiedemer [15] that the daily injection of 1 cc. of theelin is too frequent for adolescent children, causing the coagulation time to increase, whereas the administration of 1 cc. of theelin every second or third day will, in two or three weeks, bring the coagulation time down toward normal, where it can be maintained by two injections a week.

Each of two other patients (patients 3 and 6) received one subcutaneous injection of 250 rat units of follutein in order to observe the immediate effect of a single injection of the anterior pituitary-like hormone. Determinations of the coagulation time were made immediately preceding and three hours after the injection. Patient 3 had received 8 Gm. of desiccated whole ovary (derived from 48 Gm. of the fresh gland) by mouth daily for twelve days without apparent influence on the coagulation time of his blood. Before the injection of follutein his blood coagulation time was four hours and five minutes; three hours later it was five hours and five minutes. Patient 6 had received no treatment for six months. The coagulation time of his blood before the injection of follutein was six hours and forty-five minutes; three hours later it was four hours and thirty-five minutes. Patient 1 (chart 1), in a similar experiment, had a coagulation time of five hours and ten minutes before the injection and of three hours and fifty minutes three hours later. These changes in the coagulation time demonstrate no consistent tendency and indeed are scarcely beyond the limits of technical error. They cannot be interpreted to indicate an immediate effect from the injection of follutein.

Determinations of the Estrogenic and Gonadotropic Factors in the Blood and Urine.—The first determination of the estrogenic substance in a forty-eight hour specimen of urine from patient 1 (chart 1) was made from Jan. 10 to 12, 1933. The specimen contained between 12 and 20 rat units, which was the largest amount recovered from a forty-eight hour specimen of this patient's urine during the control period (period 1). The coagulation time of the blood on the day the collection of urine was started was eight hours and thirty-seven minutes, a long coagulation time, but near the beginning of a period of improved blood clotting. The next largest amount of estrogenic substance recovered was between 8 and 12 rat units in a specimen collected from March 29 to 31. On the following day the coagulation time was four hours and fifteen minutes. One week later, with from 2 to 4 rat units of estrogenic substance in a forty-eight hour specimen, the coagulation time was seven hours and forty-five minutes. In this instance, the increase in estrogenic substance in the urine occurred coincidentally with a

15. Wiedemer, quoted by Mills, C. A.: Hemophilia, J. Lab. & Clin. Med. **17**: 932 (June) 1932.

lessened coagulation time immediately preceding an increase, whereas in the former instance the diminishing coagulation time continued to decrease, as did the excretion of the estrogenic substance. Six other determinations of the excretion of estrogenic substances in forty-eight hour specimens showed values varying from less than 2 rat units, on March 20, to more than 8 rat units, on March 3, without relation to the length of the coagulation time.

Two 10 cc. specimens of urine from patient 1 tested for gonadotropic effect gave negative results. Of eight 5 cc. specimens of blood serum tested, four had a definite follicle-stimulating effect. Follutein (250 rat units) was injected subcutaneously after one positive reaction. The blood serum drawn three hours later gave a weakly positive reaction. In each instance but one, a positive follicle-stimulating effect was associated with a longer blood coagulation time than was observed when the gonadotropic factor was not demonstrated in the blood serum. The one exception was on January 10, when the serum failed to show the gonadotropic factor and the coagulation time was higher than at any of the subsequent determinations in period 1.

During the administration of luteo-hormon, in periods 2 and 3, there was a persistently high excretion of estrogenic substance which was greater than this patient had shown before starting the treatment and which was equaled only by the values obtained in one determination on the urine from a normal male and three scattered determinations on the urine of patient 5 during a control period (chart 2, period 8). These observations are in accord with the work of G. V. and O. W. Smith,[11] previously cited. No correlation could be established between the amount of the estrogenic factor excreted and the length of the coagulation time.

A determination of the excretion of the estrogenic substance in a forty-eight hour specimen of urine of patient 5 was made on Sept. 9, 1932, three months after he had received "Antuitrin S" for six days. The amount excreted was found to be more than 8 rat units. At the start of period 1 (chart 2), three days after discontinuing the daily administration of 8 Gm. of desiccated ovarian substance, the excretion of estrogenic substance in a forty-eight hour specimen was between 12 and 20 rat units. Two days later the blood coagulation time shown by the first test of period 1 was two hours and twenty-five minutes. Thereafter until the end of period 7 the excretion of estrogenic substance fluctuated from less than 2 rat units to between 4 and 8 rat units per forty-eight hour quantity of urine, regardless of the change in the coagulation time of the blood or of the therapy given. Two days after period 7, however, the excretion of estrogenic principle in a forty-eight hour specimen increased to more than 30 rat units, and it remained at a high level, while the coagulation time fell to fifty minutes and subsequently increased

to two hours, at which approximate level it remained. Determinations of the amount of estrogenic substance excreted were not carried out beyond the end of period 8.

Ten cc. of urine from patient 5 (chart 2) was tested for follicle-stimulating effect on eight occasions. Two tests were negative and one positive in period 1, before follutein was administered, and three were negative and two positive during periods 2 and 3 while follutein was being given. One 10 cc. sample of this patient's blood serum taken in period 1 produced no follicle-stimulating effect, while one 5 cc. sample gave a positive reaction. Seven 5 cc. samples of serum were tested for the follicle-stimulating effect in periods 2 to 7, inclusive. Of these, four gave negative, and two, positive reactions, and in one instance the

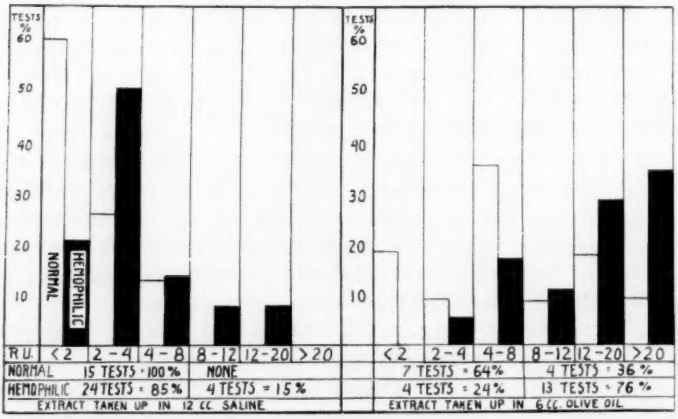

Chart 3.—A graph showing the relative amounts of estrogenic substance recovered in forty-eight hour specimens of urine of twenty-six normal males and forty-five persons with hemophilia. The white columns represent the percentage of tests on the urine of normal males yielding the indicated quantity of estrogenic substance expressed in rat units per forty-eight hour specimen of urine. The black columns represent the percentage of tests on the urine of the persons with hemophilia. The number and percentage of the specimens yielding less than 8 rat units per forty-eight hour specimen of urine and those yielding more than 8 rat units are indicated at the bottom of the chart.

effect was doubtful. In general, the positive reactions of the blood were associated with longer coagulation time than were the negative reactions. However, ten days after the end of period 7, a strongly positive reaction was obtained with blood the coagulation time of which was one hour and fifty minutes, an average time for this patient.

Determination of Estrogenic Substance in the Urine of Hemophilic and Normal Males.—The quantity of estrogenic substance contained in

forty-five specimens of urine voided over a forty-eight hour period was determined in six patients with hemophilia. Similar determinations were made on twenty-six specimens from twenty-six normal males of comparable age (chart 3). The specimen of urine from the patients with hemophilia comprising the series were collected only during control periods, while the patients were receiving no specific therapy, and in no instance were specimens included which had been passed less than eight days after therapy was discontinued.

In twenty-eight of the determinations on the urine from patients with hemophilia and in fifteen of the tests on specimens from normal subjects, the fraction of extract for injection into the test animals was taken up in 12 cc. of a physiologic solution of sodium chloride. In the tests on seventeen specimens from patients with hemophilia and on eleven specimens from normal males, 6 cc. of olive oil was used for this purpose. The yield of estrogenic substance was found to be greater with the latter technic, as is shown in chart 3.

The number of tests is too small to permit dogmatic mathematical analysis, but the recovery from the urine of the patients with hemophilia of an estrus-inducing substance has been demonstrated indisputably. The quantity of estrogenic substance excreted by some normal males, as assayed in forty-eight hour specimens of urine, was greater than that excreted by some patients with hemophilia in a similar period. Considered as a group, however, our patients with hemophilia excreted a greater amount of the substance than did our group of normal males.

CONCLUSIONS

As a result of these observations we feel confident that persons with hemophilia have no lack of estrogenic substance in their urine and, although it does not necessarily follow, probably have no deficiency of this principle in their blood. Our observations fail to substantiate the theory that an absence of this hormone is responsible for the impaired coagulability of the blood in persons with hemophilia. Conversely, we have been unable to alter the characteristic fluctuations of the prolonged coagulation time of the blood in hemophilia by the administration of estrogenic substances.

The frequency with which increases in the coagulation time of the blood were associated with a demonstrable amount of the gonadotropic factors in the blood and the somewhat increased blood coagulation time found in patient 5 while he was receiving follutein, an anterior pituitary-like gonadotropic substance, and after exposure of the pituitary region to stimulating doses of roentgen rays are observations which could be construed to indicate that the gonad-stimulating hormone of the anterior pituitary gland may contribute an adverse factor to blood clotting in hemophilia. However, the absence of demonstrable amounts of the

gonadotropic factor in the blood of persons with hemophilia while a prolonged coagulation time was maintained argues against the essential importance of this factor in influencing the coagulation time.

We have discovered no evidence to suggest that any of the hormones considered exert any fundamental influence on this sex-linked, hereditary disorder of blood clotting.

SUMMARY

Two patients with hemophilia have been studied for ten and thirteen months, respectively, while receiving no specific therapy and while receiving preparations of estrogenic substance by mouth and subcutaneously, the hormone of the corpus luteum intramuscularly and the gonad-stimulating hormone from the urine of pregnant women subcutaneously. One patient was exposed to stimulating doses of roentgen rays over the pituitary region.

The administration of such hormones to these patients with hemophilia was not associated with a demonstrable improvement in the clinical condition or with a significant diminution in the coagulation time of the blood.

Frequent determinations revealed no relationship between the fluctuation of the coagulation time of the blood and the amount of estrogenic substance recovered from forty-eight hour specimens of urine.

The urine from untreated patients with hemophilia usually contained a larger amount of estrogenic substance than did the urine from normal males of comparable age.

During the administration of the anterior pituitary-like gonadotropic hormone, after roentgen irradiation of the pituitary region and sometimes in association with a demonstrable amount of the gonadotropic factor in the blood, it took longer than usual for the blood to clot.

In view of our data we conclude that the hormones investigated in this study do not exert a fundamental influence in hemophilia.

PHYSICAL CONSTITUTION AND DISEASE

II. ABSENCE OF CORRELATION BETWEEN THE ANATOMIC CONSTITUTION AND THE PREDISPOSITION TO DIABETES MELLITUS, CHOLECYSTITIS AND PEPTIC ULCER

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When you can measure what you are speaking about and express it in numbers, you know something about it, but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind.—*Lord Kelvin.*

We shall see that the connection between physical diseases and the external configuration of the body is less close than has been assumed. . . .—*Jonathan Hutchinson: The Pedigree of Disease,* London, 1884.

Since the publication of our first paper on this subject [1] an opportunity was taken of reviewing the literature dealing with this subject in greater detail. After a thorough search of the older literature it was surprising to find how little attention had actually been paid to the matter in what could be considered a useful sense. The most plausible reason for this appears to be that for many centuries the subject was confused by the haze of the four humors, and obviously so long as constitution rested on this mythical foundation progress could not be made. What ensues is supplementary to the review given in the previous report and is the result of a search in the writings of about thirty of the better known clinicians from the Greco-Roman period of medicine onward.

The first reference to constitution with the modern meaning, in the Latin, was found in the works of Cicero [2] (106-43 B.C.). He translated *εὐσθένεια,* that is, a good state of health, as *firma corporis constitutio.*[2] The word "constitution" in the sense of "the physical nature or character of the body in regard to healthiness, strength, vitality of the body" was used in English as early as 1553.[3]

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1. Feigenbaum, J., and Howat, D.: The Relation Between Physical Constitution and the Incidence of Disease, J. Clin. Investigation **13**:122, 1934.

2. Cicero: De officiis, paragraphs 3, 33 and 117.

3. A New English Dictionary on Historical Principles, edited by James A. H. Murray, New York, Oxford University Press, 1893, vol. 2.

Celsus (53 B.C.-A.D.)[4] appears to be the first of the medical writers of note to recognize that physical constitution as such may exist and may be a factor in the etiology of disease. In the following abstract the implication may be drawn that certain physical characteristics determine the predisposition to diseases.

"But above all things everyone should know the nature of his constitution: because some are slender, others fat; some are hot, others more cold; some are moist, others dry . . . *there are very few who have not some weak part of the body.*"[5]

It was only seventeen centuries later that John Huxham (1692-1768) presented the first scientific definition of constitution, including in it the factors of heredity and environment. Huxham considered fever as the struggle of nature to relieve herself of something oppressive, and in discussing the efforts of the body to accomplish this end he maintained that the constitution of the body must be taken into account. Huxham[6] defined constitution as follows:

Probably all that we call firmness of body and strength of constitution, is originally owing to the rudimental strength and stamina of our bodies; and on the strong or weak texture of them in a great measure, depends our future prosperous or adverse health. There was indeed a determined constitution and strength of fibres designed by nature, and any deviation from it may be called a disease; which may arise from weakly parents, errors in diet, exercise, and many other things: and this deviation I would have heedfully attended to in practice.

Of all the medical writers preceding the modern period John Hunter (1728-1793) adopted the most scientific attitude toward the various aspects of constitution. About one hundred and fifty years ago he recognized the problems bound up with the subject. Curiously enough his ideas concerning constitution are not referred to by students of the subject whose work has been consulted. It is therefore worth while to examine Hunter's views in some detail.

Hunter[7] believed that the interaction between the particular constitution of the human body and pathologic influences was responsible for the symptoms and signs of disease. He indicated this in the following roundabout and whimsical manner. "The most simple idea I can form of an animal being capable of disease is, that every animal is endued with a power of action and a susceptibility of impression, which impression forms a disposition, which disposition may produce action,

4. Celsus, cited by Huxham.[6]

5. Celsus, Aurelius Cornelius: On Medicine, London, E. Cox, 1831, vol. 1, p. 34.

6. Huxham, John: An Essay on Fevers to Which is Now Added a Dissertation on the Malignant Ulcerous Sore-Throat, ed. 4, London, J. Hinton, 1764, p. 27.

7. Hunter, John: The Works of John Hunter with Notes, edited by J. F. Palmer, London, Longman, Rees, Orme, Brown, Green and Longman, 1835, vol. 1, p. 34.

which action becomes the immediate sign of the disease." It has been recognized by all workers interested in the subject that, whatever may be responsible for the varieties of reaction to disease, these could not easily be altered by artificial means. Hunter expressed this opinion in the following excerpt: "The susceptibility of the constitution may be increased, so as almost to be similar to a new formation, but is never originally formed by art." [8] "Art" is taken to imply environmental circumstances or treatment. With the foregoing two preliminary views Hunter proceeded to emphasize the fact that certain systems in a person may show a greater susceptibility to disease than others. "Thus as the liver in some constitutions is more susceptible to secreting bile, which is its natural action, than it is in others, so also it is more susceptible of its peculiar diseases in some constitutions than it is in others." [9] And the following observation would not be out of place in a modern textbook of bacteriology, with the underlying explanation of the phenomenon still absent, however. "Two men equally susceptible may be exposed to the cause of an ague: one may have the disease, the other not." [10] Moreover, the tendency of certain persons to display mild or violet reactions to disease-producing influences is stated: "For example, some constitutions are more susceptible of inflammatory fevers than of any other fevers; others are more susceptible of putrid fevers (e. g., typhoid fever); while either one or the other of these constitutions might have some other disease, either violently or mildly, as smallpox, measles, etc." [8] Furthermore, it is important to appreciate that Hunter realized the complex nature of constitution and that he saw the numerous phases of its application to the study of disease.

There is a reference in Hunter's work—the first, so far as can be determined—to the effect of the complexion on the incidence of disease. "Fair people are also more susceptible of certain diseases than the dark, as of scrofula . . . The irritable inflammation also is more common in the fair than the swarthy." [11]

It is evident that the historical background of constitution, as understood at present, dates back only about a century and a half. Moreover, the unquestioned father of the subject is John Hunter, who in his works pointed the way to numerous problems. But constitution did not become a problem for serious investigation until about one hundred years later. Indeed it is discouraging to find how little progress has been made in this subject since it was first placed on a scientific basis by Hunter.

8. Hunter,[7] p. 303.
9. Hunter,[7] p. 304.
10. Hunter,[7] p. 306.
11. Hunter,[7] p. 308.

The current opinion in the past century has been that a person's physical build is one of the factors responsible for his predisposition to a particular disease. This view leads to what has been referred to as the physiognomic diagnosis of disease or disease groups. It represents a long-standing clinical tradition and is based in effect on a *post hoc ergo propter hoc* fallacy. Because a patient suffering from diabetes mellitus may have a certain physical configuration this habitus is said to make him more susceptible to the development of the disease. A more common example perhaps is the view long accepted that the flat thorax of a patient with pulmonary tuberculosis has made him more susceptible to phthisis. It is erroneous to draw such a conclusion, because the disease itself may have produced the changes observed in the thorax, and these may be simply *manifestations* of the disease. There is little doubt that many attributes of the body which have been said to render a person displaying them susceptible to a certain disease have actually been produced by the disease.

In bringing about the change of attitude from belief in the humoral to that in the morphologic predisposition Addison and Hutchinson in England, di Giovanni and Pende in Italy, Kretschmer in Germany, Bauer in Vienna and Draper in the United States all played a prominent rôle. Although the study of physical constitution does not represent the solution of the problem, nevertheless it points the direction for further study of the patient along strictly objective lines. Any one who is at all familiar with the long and involved history which attaches to the subject realizes that this changed attitude toward the problem represents a major advance. It is in this respect that the workers just mentioned made their chief contribution to the study of the subject. Draper brought the work to the point at which he believed that many individual diseases had specific diatheses or types which could be recognized by anthropometric methods. It was at this juncture that the present studies of the subject were undertaken.

The greater part of the work reported here has been alluded to in the previous communication [1] in some detail. It is proposed to analyze the results further in this paper, particularly so far as comparing them with the figures obtained by Draper is concerned.

In all, 192 patients were employed for the anthropometric measurements. Seventy-nine patients were diabetic, 67 suffered from peptic ulcer, and 46 from cholecystitis. Ninety-one were males, and 101 were females. The age groups and the racial distribution were sufficiently alike in the three disease entities to be disregarded without fear of interfering with the validity of the results. Thirty-seven measurements were taken, including various diameters of the head, extremities and trunk. In the case of bilateral measurements of the extremities only the diameters on the left side were obtained. In addition, eight indexes were calculated from the data available. These were worked out only in the instances in which a single diameter of a portion of the body by itself would not convey the complete picture. Since in appraising the various measurements obtained males could be

compared only with males and females with females, the groups with each of the three diseases had to be subdivided into the male and female components, so that six major groups were dealt with statistically.

The statistical methods employed need not be considered in detail here, but the following brief comment will clarify much of the discussion that is to follow. In the first place, the mean or average was obtained for each pair of the three groups. Then the differences between the diabetic group and that with peptic ulcer, between the group with peptic ulcer and that with cholecystitis, and between the diabetic group and that with cholecystitis were worked out for both males and females. The standard error of the difference was calculated, and the difference obtained was divided by the standard error. When the quotient (t) equaled or exceeded 2 the difference was taken to be of some significance. But in order to eliminate all doubt, in the final tables the difference in the same direction had to be present in both the males and the females of the groups compared before it was regarded as actually significant.

A summary of the results is given in table 1. A few of the results may be discussed here, so that the remainder of the table may be studied with greater ease. The upper facial diameter, or the interval between the most prominent part of the maxilla on each side, of the female diabetic patients was found to be greater than that of the female patients with peptic ulcer. But this difference was not observed in the males. In contrast the nasion prosthion (the distance between the bridge of the nose and the interval between the incisor teeth) of the male patients with pepti. ulcer was longer than that of the male diabetic patients, but this difference failed to appear in the female patients. Likewise the nasion prosthion was greater in the males with peptic ulcer than in those with cholecystitis, but the difference between the females of these groups was insignificant. The first measurement in the table to show a significant difference for both the males and the females of corresponding disease groups is the bigonial diameter, or the distance between both angles of the mandible. This measurement was greater in the diabetic patients than in those with peptic ulcer. It will be observed that the length of the neck in both the male and the female patients with peptic ulcer is greater than in the diabetic groups. Scrutiny of the complete table reveals that there were significant differences between the various measurements and the diameters in 53 cases, or 19 per cent of the total, but that the males and females differed in the same direction in only 9 instances (18 measurements), or 6.6 per cent. The latter figure is a negligible quantity as far as probabilities in statistical work are concerned. It can be stated categorically that the physical constitution of a patient is not a deciding factor in the etiology of peptic ulcer, cholecystitis and diabetes.

It is relevant to introduce here a warning regarding the interpretation of graphic figures in work of this nature. Unfortunately, graphs can be made to support almost any preconceived hypothesis, depending entirely on the opinions of the author. It is not so with the statistical method adopted in the present study.

TABLE 1.—*List of Body Measurements in Which Significant Differences Were Obtained* *

Measurement	Sex	Direction of Differences Between Disease Groups
Facial diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Nasion prosthion	M	Value in patients with peptic ulcer greater than in those with diabetes
Nasion prosthion	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Length of ear	F	Value in diabetic patients greater than in those with peptic ulcer
Length of ear	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Horizontal length of mandibular ramus	F	Value in diabetic patients greater than in those with peptic ulcer
Horizontal length of mandibular ramus	F	Value in diabetic patients greater than in those with cholecystitis
Bigonial diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Bigonial diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Bigonial diameter	M	Value in patients with cholecystitis greater than in those with peptic ulcer
Circumference of neck	M	Value in diabetic patients greater than in those with peptic ulcer
Length of neck	M	Value in patients with peptic ulcer greater than in those with diabetes
Length of neck	F	Value in patients with peptic ulcer greater than in those with diabetes
Length of neck	F	Value in patients with cholecystitis greater than in those with diabetes
Thoracic anteroposterior diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Thoracic anteroposterior diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Thoracic anteroposterior diameter	F	Value in diabetic patients greater than in those with cholecystitis
Thoracic lateral diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Thoracic lateral diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Thoracic lateral diameter	F	Value in patients with cholecystitis greater than in those with peptic ulcer
Biacromial diameter	F	Value in patients with cholecystitis greater than in those with diabetes
Biacromial diameter	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Circumference of chest	M	Value in diabetic patients greater than in those with peptic ulcer
Circumference of chest	F	Value in diabetic patients greater than in those with peptic ulcer
Circumference of chest	M	Value in patients with cholecystitis greater than in those with peptic ulcer
Circumference of chest	F	Value in patients with cholecystitis greater than in those with peptic ulcer
Length of chest	M	Value in diabetic patients greater than in those with cholecystitis
Umbilical xiphoid diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Breadth of nail	M	Value in patients with peptic ulcer greater than in those with diabetes
Breadth of nail	M	Value in patients with cholecystitis greater than in those with diabetes
Breadth of hand	F	Value in diabetic patients greater than in those with cholecystitis
Circumference of leg	M	Value in diabetic patients greater than in those with peptic ulcer
Length of radius	F	Value in diabetic patients greater than in those with cholecystitis
Length of tibia	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Weight	M	Value in diabetic patients greater than in those with peptic ulcer
Weight	M	Value in patients with cholecystitis greater than in those with peptic ulcer
Upper facial index†	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Upper facial index	F	Value in patients with cholecystitis greater than in those with diabetes
Lower facial index‡	M	Value in patients with peptic ulcer greater than in those with diabetes
Lower facial index	M	Value in patients with peptic ulcer greater than in those with cholecystitis

* A quotient (t) equal to 2 or higher was considered significant.

† The upper facial index equals $\frac{\text{Nasion prosthion}}{\text{Facial diameter}}$

‡ The lower facial index equals $\frac{\text{Nasion submenton}}{\text{Bigonial diameter}}$

TABLE 1.—*List of Body Measurements in Which Significant Differences were Obtained *—Continued*

Measurement	Sex	Direction of Differences Between Disease Groups
Index of neck	M	Value in patients with peptic ulcer greater than in those with diabetes
Index of neck	F	Value in patients with peptic ulcer greater than in those with diabetes
Index of neck	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Index of neck	F	Value in patients with cholecystitis greater than in those with diabetes
Thoracic index I §	M	Value in diabetic patients greater than in those with peptic ulcer
Thoracic index I	F	Value in diabetic patients greater than in those with cholecystitis
Thoracic index II ‖	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Thoracic index II	F	Value in patients with peptic ulcer greater than in those with diabetes
Thoracic index II	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Umbilical index	M	Value in patients with peptic ulcer greater than in those with diabetes
Arm-leg index	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Arm-leg index	M	Value in diabetic patients greater than in those with cholecystitis
Ponderal index	M	Value in diabetic patients greater than in those with peptic ulcer

§ The thoracic index I equals $\frac{\text{Thoracic anteroposterior diameter}}{\text{Thoracic length}}$

‖ The thoracic index II equals $\frac{\text{Thoracic length}}{\text{Thoracic circumference}}$

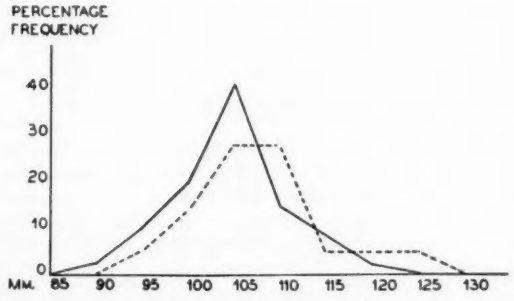

Chart 1.—Curves for the bigonial diameter in male patients. The solid line represents the figures for a group of 55 patients with peptic ulcer; the dash line, those for a group of 27 patients with diabetes. The interesting features of these curves are the flattened top of the curve for the diabetic group and the long span of the descending limb. As in the data shown in other charts, t was significant.

We have included four charts to illustrate the difficulty referred to. In each instance, t was found to exceed 2; nevertheless no one criterion can be chosen to interpret the figures. This is especially applicable in cases in which the differences are on the borderline of significance. Therefore, this fact must be borne in mind in all work on physical constitution in which statistical analysis plays a part, and the graphic figures alone cannot be accepted.

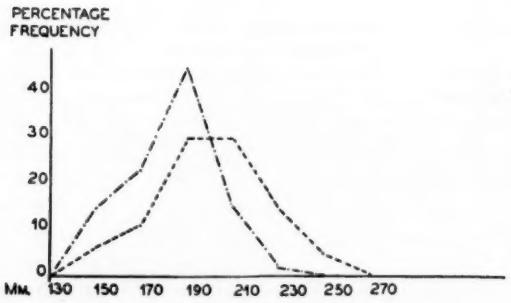

Chart 2.—Curves for the thoracic anteroposterior diameter in female patients. The dot-and-dash line represents the figures for a group of 52 patients with diabetes; the dash line, those for a group of 37 patients with cholecystitis. Note again the flat top of the curve for the group with cholecystitis. This type of curve is uncommon in biometric statistics.

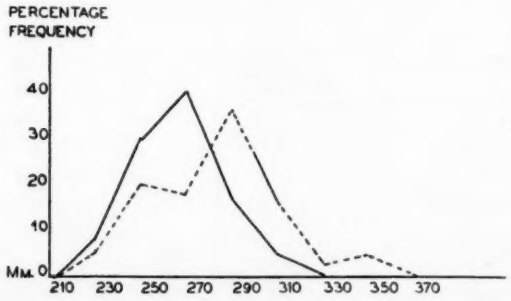

Chart 3.—Curves for the thoracic lateral diameter in male patients. The solid line represents the figures for a group of 55 patients with peptic ulcer; the dash line, those for a group of 27 patients with diabetes. The noteworthy features in this chart are the three peaks of the curve for the diabetic group and the comparatively small area of overlapping apparent, as compared with the curves shown in the other charts.

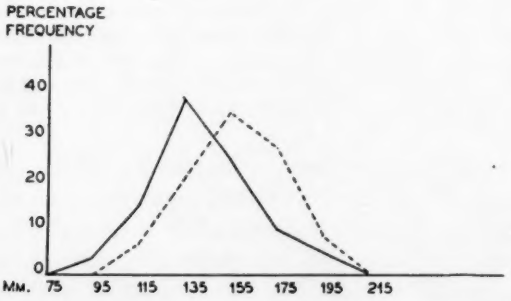

Chart 4.—Curves for the umbilical-xiphoid diameter in male patients. The solid line represents the figures for a group of 51 patients with peptic ulcer; the dash line, those for a group of 27 diabetic patients. These curves are the most representative of all those obtained and indicate a sample of the usual graphs for biometric measurements.

From the point of view of a check on the present work it has been especially helpful to turn to Draper's studies on physical constitution incorporated in his first book on this subject.[12] Tables with the figures

TABLE 2.—*Comparison of Average Measurements for Our and Draper's Series* *

Measurement	Sex	Patients with Peptic Ulcer		Patients with Cholecystitis	
		Our Series	Draper's Series	Our Series	Draper's Series
Cephalic length	M	180	191	179	194
Cephalic length	F	174	182	172	182
Cephalic breadth	M	144	150	145	157
Cephalic breadth	F	139	146	142	149
Length of ear	M	67	65	69	68
Length of ear	F	59	60	61	60
Breadth of ear	M	29	34	28	37
Breadth of ear	F	27	30	27	34
Nasion prosthion	M	70	71	66	70
Nasion prosthion	F	62	68	64	65
Facial diameter	M	110	138	112	142
Facial diameter	F	102	130	105	132
Bigonial diameter	M	105	105	111	105
Bigonial diameter	F	98	97	101	99
Ascending ramus of mandible	M	55	68	58	72
Ascending ramus of mandible	F	49	61	51	67
Horizontal ramus of mandible	M	94	92	98	96
Horizontal ramus of mandible	F	87	91	87	87
Length of neck	M	119	162	108	167
Length of neck	F	101	149	98	143
Circumference of neck	M	338	349	343	391
Circumference of neck	F	317	323	324	342
Thoracic anteroposterior diameter	M	195	206	204	231
Thoracic anteroposterior diameter	F	175	195	184	215
Thoracic lateral diameter	M	266	271	273	294
Thoracic lateral diameter	F	239	195	266	266
Circumference of chest	M	818	875	860	962
Circumference of chest	F	759	825	818	883
Length of chest	M	181	316	190	320
Length of chest	F	164	294	164	288
Biacromial diameter	M	380	377	375	387
Biacromial diameter	F	352	337	339	344
Length of arm	M	748	739	753	884
Length of arm	F	678	651	663	665
Length of humerus	M	301	312	308	312
Length of humerus	F	281	266	277	272
Length of radius	M	262	245	255	249
Length of radius	F	233	217	225	205
Umbilical-xiphoid diameter	M	142	209	148	219
Umbilical-xiphoid diameter	F	155	201	158	215
Distance from umbilicus to pubis	M	145	160	140	145
Distance from umbilicus to pubis	F	150	150	150	155
Bi-iliac diameter	M	233	285	234	299
Bi-iliac diameter	F	234	286	236	293
Length of lower extremity	M	877	903	898	913
Length of lower extremity	F	813	818	785	822
Length of femur	M	406	467	416	464
Length of femur	F	388	424	370	422
Length of tibia	M	398	363	405	379
Length of tibia	F	379	329	352	334
Height of foot	M	72	73	76	71
Height of foot	F	55	65	65	67
Weight	M	58	59	66	77
Weight	F	57	55	63	72

* The measurements are given in millimeters.

of measurements corresponding to those taken in this work are given in his study. Table 2 is a comparison of the figures obtained by Draper and by us.

12. Draper, G.: Human Constitution: A Consideration of Its Relationship to Disease, Philadelphia, W. B. Saunders Company, 1924.

As for table 1, it is advisable to analyze certain features in this list with a view to facilitating the analysis of the whole table by the individual reader. The first difference of any importance occurs in the facial diameter. One notes that the average for Draper's figures is 28 mm. greater for the male patients with peptic ulcer and 30 mm. greater for the males with cholecystitis. Similarly for the female group Draper's figures show an increase of 28 mm. for the patients with peptic ulcer and of 27 mm. for those with cholecystitis. It is important to note, however, that though there are differences between the two sets of figures these differences are small. The explanation of the discrepancy observed is undoubtedly that the surface markings and the technic employed by the investigators differed in some respects. In considering the length of the neck even larger differences are observed, but the same factor can account for them. It is more difficult to explain the difference occurring in the thoracic anteroposterior diameter. In this case Draper's male patients with cholecystitis showed a diameter 27 mm. greater than ours, while the female patients with cholecystitis showed an increase of 31 mm. The patients with peptic ulcer did not show this difference. The next striking discrepancy is to be found in the length of the chest. Obviously the landmarks in that measurement must have been different. The arm length of the male patients with cholecystitis was fully 131 mm. greater in Draper's than in the present series, but no such divergence is present in any of the three other comparisons in arm length. The variations in the umbilical-xiphoid diameter can be explained by the fact that the points selected by Draper and by us probably differed. The same applies no doubt to the bi-iliac diameter and to the femoral and tibial lengths. With these facts in mind it is apparent that on the whole the two sets of figures are comparable. And it is reasonable to suppose that, had Draper's figures received the statistical treatment accorded the figures of the present work, he would have reached the same conclusion.

Some interesting contributions have been added recently to the current literature on constitution. The following are perhaps the most representative of the point of view expressed in this report. Millard Smith,[14] in a comprehensive study of 102 cases of atrophic arthritis, was unable to find any particular type as characteristic of the disease. A rough classification of habitus showed that his patients fell into the following groups: asthenic, 49; intermediate, 29; sthenic, 24. Moreover the complexion of the whole group was not at all distinctive. Hess and Blackberg,[15] in work which involved the production of rickets in puppies,

13. This footnote was deleted by the author.

14. Smith, Millard: A Study of One Hundred and Two Cases of Atrophic Arthritis, New England J. Med. **206**:103, 1932.

15. Hess, A. F., and Blackberg, S. N.: Constitutional Factors in the Etiology of Rickets, Am. J. Physiol. **102**:8, 1932.

concluded that the element of constitution, although important in etiology, did not reside in the physical type of the animal.

Some very important as well as thorough and careful work was published recently by Matthew Young [16] from the Institute of Anatomy at University College, London. He studied the physical type of a large number of children with asthma and rheumatism (rheumatic fever?), using a third group of normal children as a control. There were 1,212 children in all. Their ages varied between 6 and 12 years, and from a comparison of the average measurements the children were divided into three two-year groups. Thirty measurements as well as notes regarding the complexion and posture were obtained for each child. The averages, frequency, distributions and variabilities were worked out for the three groups. The conclusion he arrived at is well worth quoting:

> The differences in the three groups of children, the asthmatic, the rheumatic and the normal, in respect of the aggregate of physical characters brought under review are relatively so slight that they cannot be considered to support the view that asthmatic and rheumatic children really differ on the average from one another or from the general population of children from which they are drawn in bodily conformation or physical type, though they may possibly, indeed probably, differ in other constitutional traits.

In order to make headway in the study of constitution it will be necessary to step from a consideration of physical constitution, which appears irrelevant, to a consideration of other aspects. In the case of bacterial diseases the immunologic factors which determine the reaction between bacteria and the animal body must be investigated, while in the case of degenerative and metabolic diseases the factors which determine the speed of biochemical processes must be studied. At all events, the opinion held until now of the importance of the physical habitus in the production of disease should be changed.

SUMMARY AND CONCLUSIONS

A supplementary historical review of the place occupied by constitution in the study of disease is presented. The contributions of Celsus, Huxham and John Hunter are indicated. There is little doubt that Hunter's opinions of constitution were closer to those generally held today than those of any medical writer in history, and in this respect Hunter should be regarded as the "father of constitution."

The conception that the physical constitution of a person is an important factor in the etiology of disease arose from observations of the effects of certain diseases on the body. At no time were these effects controlled in investigating the subject. Thus a clinical impression

16. Young, Matthew: A Study of Rheumatic and Asthmatic Children with Special Reference to Physical Type, J. Hyg. **33**:435, 1933.

which is erroneous, namely, that the anatomic habitus is one of the causes of disease, was perpetuated.

One hundred and ninety-two patients were observed in this work. Of these 91 were males and 101 were females; 79 patients were diabetic; 67 had peptic ulcer, and 46 had cholecystitis; thirty-seven measurements were taken on each patient, and eight indexes were obtained from the measurements. The diameters and the indexes were all subjected to statistical computations. The results showed that with a few exceptions there were no anatomic characteristics distinctive of patients with diabetes mellitus, peptic ulcer or cholecystitis.

A comparison between the figures obtained by Draper in 1924 and those obtained by us points, on the whole, toward agreement. Opposite conclusions were reached because of the different statistical approach. Young's recently published careful observations on 1,212 children likewise indicate that physical constitution is not related to disease.

Dr. W. W. Francis, librarian of the Osler Library, assisted in the search through the older medical literature.

ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION

REVIEW OF ONE HUNDRED AND SEVEN CLINICAL CASES AND ONE HUNDRED AND EIGHT CASES PROVED AT NECROPSY

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The number of clinical, pathologic and experimental observations published on coronary occlusion, its effect and its recognition attest the interest that exists in the subject and its importance as a clinical problem. The very multiplicity of these observations gives rise to the need for their critical evaluation and integration. It is the purpose of this article to make such an integration.

ANATOMIC CONSIDERATIONS

The first requisite to an understanding of the problem of coronary occlusion is a certain fundamental knowledge of the anatomy of the coronary arteries in the heart of man. The work of Whitten,[1] Gross[2] and Spalteholz[3] on the coronary circulation covers the subject exhaustively. The anterior descending branch of the left coronary artery supplies the anterior portion of the left ventricle and apex and the anterior two thirds of the interventricular septum and gives off a few branches to supply a narrow zone of the anterior portion of the right ventricle. The circumflex branch of the left coronary artery supplies the left third or half of the posterior region of the basal three fifths of the left ventricle. The terminal portion of the right coronary artery, if it has its normal distribution, supplies the posterior third of the interventricular septum and the posterior basal portion of the left ventricle. This distribution of the three main arterial branches establishes three regions of the left ventricle which are the usual sites of myocardial infarction. The anterior apical region and the posterior basal region are the common sites of infarction. In a certain percentage of cases the circumflex

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A résumé of the material in this article was presented before the American Heart Association, Cleveland, June 12, 1934.

1. Whitten, M. B.: The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction, Arch. Int. Med. **45**:383 (March) 1930.

2. Gross, Louis: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, Inc., 1921.

3. Spalteholz, Werner: Die Arterien der Herzwand, Leipzig, S. Hirzel, 1924.

branch of the left coronary artery supplies the posterior basal portion of the left ventricle and the adjacent interventricular septum as well as its usual zone of ventricular muscle. Occlusion of a vessel having such a distribution will result in infarction in the posterior basal portion of the left ventricle and the adjacent interventricular septum.

PATHOLOGY OF MYOCARDIAL INFARCTION

Knowledge of certain facts of pathology is essential to an understanding of the problem of myocardial infarction. A coronary vessel may be occluded suddenly, usually by thrombosis in situ, rarely by an embolus. This results in a more or less complete destruction of the tissue in the area that was formerly supplied by the occluded vessel. A mural thrombus frequently forms beneath the myocardial infarction, particularly when the infarction involves the anterior and apical portion of the left ventricle. The presence of an organized thrombus at necropsy beneath a thin fibrous portion of cardiac muscle is strongly presumptive evidence that one is dealing with the healed stage of acute myocardial infarction, in contradistinction to chronic ischemic myofibrosis, which is considered later. Aneurysmal dilatation of the ventricular wall is almost always a sequel of an acute myocardial infarction. Localized pericarditis is observed in 13.8 per cent of cases [4] of acute myocardial infarction, and the presence of chronic pericarditis overlying a region of fibrous replacement in the myocardium is almost certain evidence that the infarction occurred as a result of acute coronary occlusion.

The common cause of chonic fibrosis of the heart muscle is coronary sclerosis. As the degree of this fibrosis is roughly proportional to the degree of narrowing of the main coronary branch supplying the portion affected, it is assumed that the fibrosis results from gradual ischemia. The term "chronic dystrophic fibrosis" is reasonably satisfactory for, and actually suggestive of, such a mechanism. Although gradual narrowing or actual occlusion of the terminal branches of the coronary vessels comes to mind as a possible explanation of scattered fibrous replacement, there are no convincing studies indicating that it is explained by either process, except in a few isolated instances. Localized regions of myocarditis which have healed have to be considered as a cause of localized fibrosis, but the absence of cells characteristic of inflammation in and about these fibrotic regions in cardiac muscle does not support such an assumption. On the other hand, it must be admitted that scattered fibrous replacement occurs in hearts in which the degree of narrowing in the main coronary branches which can be demonstrated anatomically seems hardly sufficient to account for ischemic degeneration. Whether

4. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8**:245 (Sept.) 1929.

the degree of anatomic narrowing is an accurate index of the degree of functional impairment of the diseased vessel, however, is an open question.

Although this chronic dystrophic fibrosis of the myocardium usually can be distinguished from acute infarction, especially if one bears in mind the criteria of acute infarction just cited, there are instances in which such a distinction is impossible. Particularly may this be true if acute infarction is superimposed on chronic infarction.

There is much to make one believe that occasionally coronary thrombosis occurs gradually, the vessel not becoming completely occluded for from one to three days. This may explain some instances of the delayed appearance of electrocardiographic changes indicative of infarction. I have observed a patient with a classic clinical picture of acute coronary occlusion resulting in death after seven hours. At necropsy, painstaking dissection revealed marked narrowing of the anterior descending branch of the left coronary artery, but no coronary occlusion was present. There were no changes in the myocardium indicative of acute infarction. Unfortunately, no electrocardiograms were taken in this case. It is an open question whether, had the patient recovered, electrocardiographic evidence of coronary occlusion would have been present. This suggests the possibility that in rare instances the absence of electrocardiographic signs of acute infarction following the clinical signs of acute coronary occlusion is an accurate index showing that actual occlusion and acute myocardial infarction did not occur. The only legitimate basis for contending that the electrocardiogram fails to reveal evidence of coronary occlusion rests on cases in which electrocardiographic evidence of acute coronary occlusion is lacking and in which the presence of acute myocardial infarction is proved by necropsy.

Acute myocardial infarction is almost entirely confined to the left ventricle and the interventricular septum.[5] Whitten advanced some anatomic explanations for that fact. Ball and I [5a] showed that infarction of the posterior basal portion of the left ventricle is approximately as common as is infarction of its apex and anterior portion. In the same investigation it was shown that occlusions of the right coronary artery and of the circumflex branch of the left coronary artery were much more frequent than is commonly supposed. We concluded that it is inaccurate to designate the anterior descending branch of the left coronary artery as the artery of coronary occlusion.

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5. (*a*) Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in 1,000 Consecutive Postmortem Examinations, Am. J. M. Sc. **183**:215 (Feb.) 1932. (*b*) Parkinson, John, and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), Heart **14**:195 (Aug.) 1928.

Multiple infarctions of the left ventricle are not infrequently observed, and especially is that true in fatal cases. The presence of multiple infarctions confuses the analysis of the resulting electrocardiographic changes, and in the final interpretation of such cases all possible infarcts must be sought for and their age sequence determined, if possible, by macroscopic and microscopic study.

EXPERIMENTAL STUDIES

There have been a great number of studies concerned with the electrocardiographic changes resulting from acute infarction produced experimentally. Gilchrist and Ritchie [6] pointed out that "after injecting silver nitrate into the wall of the left ventricle or interventricular septum,[7] crushing or cutting the apex of the heart,[8] or ligating the coronary arteries and their branches,[9] the electrocardiogram may become transiently monophasic, the R T segment may become deviated from the iso-electric level, or there may be negativity of T which is greatest when the interference with the blood supply of the left ventricle is most pronounced." Furthermore, in axial leads it has been shown that a negative effect on the T wave is produced by cooling the left ventricle,[10] by freezing the right ventricle,[10a] by ligating the

6. Gilchrist, A. R., and Ritchie, W. T.: The Ventricular Complexes in Myocardial Infarction and Fibrosis, Quart. J. Med. **23**:273 (April) 1930.

7. (*a*) Clerc, A.: Anomalies électrocardiographiques au cours de l'oblitération coronarienne, Presse méd. **35**:499 (April 20) 1927. (*b*) Eppinger, H., and Rothberger, C. J.: Zur Analyse des Elektrokardiogramms, Wien. klin. Wchnschr. **22**:1091 (Aug. 5) 1909.

8. Samojloff, A.: Weitere Beiträge zur Elektrophysiologie des Herzens, Arch. f. d. ges. Physiol. **135**:417 (Dec. 5) 1910.

9. (*a*) Danielopolu, D.: L'angine de poitrine et l'angine abdominale, Paris, Masson & Cie, 1927. (*b*) Gold, Harry; de Graff, A. C., and Edward D. J.: On the R-T Interval in Experimental Coronary Occlusion, Proc. Soc. Exper. Biol. & Med. **23**:664 (May) 1926. (*c*) Lewis, Thomas: The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, Heart **1**:98, 1909-1910. (*d*) Otto, H. L.: The Extracardial Nerves: An Experimental Study of Coronary Obstruction, Am. Heart J. **4**:64 (Oct.) 1928. (*e*) Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Studies, Arch. Int. Med. **22**:8 (July) 1918. (*f*) Smith, F. M.: Further Observations on the T-Wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, ibid. **25**:673 (June) 1920.

10. (*a*) Otto, H. L.: The Action of Cold upon the T-Wave of the Electrocardiogram, J. Lab. & Clin. Med. **14**:718 (May) 1929. (*b*) Smith, F. M.: Some Observations on the Effects of Heat and Cold on the Ventricles and the T Deflection of the Electrocardiogram, Heart **10**:391, 1923. (*c*) Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle-Branch Block and of the Refractory Period of the Heart of the Dog, ibid. **8**:229 (May) 1921. Eppinger and Rothberger.[7b]

right coronary artery,[11] by bringing about acute right ventricular strain,[12] by stimulating the right accelerator nerve [13] and by injecting alcohol (95 per cent) into the right ventricle.[14] A positive effect on the T wave was produced by cooling the right ventricle,[15] by freezing the left ventricle,[10a] by ligating the circumflex branch of the left coronary artery,[11] by effecting acute left ventricular [16] strain, by stimulating the left accelerator nerve [13] and by injecting mercuric chloride or silver nitrate into the right ventricle.[7b] A high take-off of the R T component of the electrocardiogram was observed following the injection of mercuric chloride, silver nitrate or alcohol (95 per cent) into the left ventricle,[17] whereas a low origin of the S T component from the S wave occurred when these substances were injected into the right ventricle. Otto,[11] using an axial lead, found that ligation of the circumflex branch of the left coronary artery of the dog (this artery supplies the left ventricle exclusively) increased the positivity of the T wave and ligation of the right coronary artery (supplying the right ventricle) caused increased negativity of the T wave, whereas ligation of the anterior descending branch of the left coronary artery (supplying the right and left ventricles about equally) produced effects partially characteristic of each of the first two types of ligation.

Smith,[9e] in 1918, studied the effects of ligation of the coronary vessels of the dog on the electrocardiogram. He observed remarkable changes in the direction and height of the T wave but did not emphasize significant changes in the level of the R S-T segment. He found that ligation of the right coronary artery did not appreciably affect the direction of the T wave. Parkinson and Bedford [5b] concluded from this and from their clinical studies that "all available evidence points to the fact that it is occlusion of the left coronary artery or its branches that produces characteristic T wave changes." Smith, in his original work, did not carry out control experiments in which the pericardium was manipulated, but the coronary arteries were not molested, to determine the effect of pericardial injury on the electrocardiogram.

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11. Otto, H. L.: The Effect of Obstruction of Coronary Arteries upon the T-Wave of the Electrocardiogram, Am. Heart J. **4**:346 (Feb.) 1929.

12. Daly, I. De B.: The Influence of Mechanical Conditions of the Circulation on the Electrocardiogram, Proc. Roy. Soc. Med. **5**:279, 1923-1924.

13. Otto, H. L.: The Extracardial Nerves: III. Further Observations upon the Relation of the Extracardial Nerves to Heart-Block, Am. Heart J. **4**:59 (Oct.) 1928.

14. Otto, H. L.: The Ventricular Electrocardiogram: An Experimental Study, Arch. Int. Med. **43**:335 (March) 1929.

15. Eppinger and Rothberger.[7b] Otto.[10a] Smith.[10b] Wilson and Herrmann.[10c]

16. Otto, H. L.: The Effect of a Sudden Increase in the Intracardiac Pressure upon the Form of the T-Wave of the Electrocardiogram, J. Lab. & Clin. Med. **14**:643 (April) 1929. Daly.[12]

17. Otto.[14] Eppinger and Rothberger.[7b]

The work by Whitten and me [18] indicated that occlusion of the right coronary artery producing infarction in the posterior basal portion of the left ventricle caused just as characteristic electrocardiographic changes as did occlusion of the anterior descending branch of the left coronary artery. We pointed out that it was the situation of the infarction and not the vessel which was occluded that determined the type of electrocardiographic pattern obtained.

Mann and I [19] undertook experiments to determine whether experimental occlusion of the right coronary artery of the dog produced deviations of the R S-T segment. In control experiments in which the pericardium was opened but in which the coronary vessels were not disturbed, we obtained all the changes in the T wave described by Smith [9e] in his original experiments on ligation, but no significant deviation of the R S-T segment resulted. When the posterior circumflex branch or branches of the left coronary artery or a large branch or branches of the right coronary artery were ligated, marked deviation of the R S-T segment in leads I and III followed in the first forty-eight hours. No attempt was made to explore the various possible sites of infarction in order to determine their correlated electrocardiographic changes. The evidence seemed conclusive that ligation of the right coronary artery produced just as marked changes in the R S-T segment as did ligation of the left coronary artery. The results of these experiments are open to the criticism that it is difficult to exclude the effects of pericardial injury on the R S-T segment and to the further criticism that the areas of ischemia produced by ligation were quite large.

Feil, Katz, Moore and Scott [20] found no change in the R S-T segment of the electrocardiogram after ligating the anterior descending branch of the left coronary artery unless, in addition, they clamped the inferior vena cava. They concluded that "R S-T deviation is a manifestation of myocardial ischemia in the production of which coronary occlusion is one factor." They believe that, in addition to coronary occlusion, a reduction in blood pressure was necessary to effect this change in the electrocardiogram. Wood and Wolferth [21] differed with that opinion, and they concluded from their experiments that no additional impairment of the coronary circulation other than that produced

18. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, Am. Heart J. **5**:142 (Dec.) 1929.

19. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, Am. Heart J. **7**:477 (April) 1932.

20. Feil, H. S.; Katz, L. N.; Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, Am. Heart J. **6**:522 (Feb.) 1931.

21. Wood, F. C., and Wolferth, C. C.: Experimental Coronary Occlusion: Inadequacy of the Three Conventional Leads for Recording Characteristic Action Current Changes in Certain Sections of the Myocardium; An Electrocardiographic Study, Arch. Int. Med. **51**:771 (May) 1933.

by occlusion of a coronary artery was necessary for the production of deviation of the R S-T segment, with which observation Mann's and my experience was in agreement. Wood and Wolferth further found that the difficulty in obtaining electrocardiographic changes following ligation of the anterior descending branch of the left coronary artery was partially obviated if they did not work with the anterior aspect of the heart exposed, a condition that diminished conduction of the action currents from the heart. More significantly, they found that by means of an anteroposterior thoracic lead, in addition to the conventional leads, it was easy to demonstrate that ligation of the anterior descending branch produced changes in the R S-T segment just as promptly as did ligation of other branches of the coronary vessels.

On the basis of clinical observations it does not appear that a fall in blood pressure is essential to the production of changes in the R S-T segment. These changes frequently are not observed within the first twenty-four hours after coronary occlusion, at a time when the greatest fall in the patient's blood pressure has occurred. Moreover, their classic development a few days later occurs frequently when the blood pressure is rising or has reached the preinfarction level. The picture of cardiac failure, as manifested by edema, dyspnea or cyanosis, is conspicuous by its absence in the average case even for some days after coronary occlusion unless the patient is approaching death. Marked deviations of the R S-T segment frequently develop in cases of mild and nondisabling attacks of coronary occlusion, whereas minimal R S-T deviation alone, sometimes so slight as to make it difficult to recognize the change as evidence of acute infarction, frequently develops when the attack is so grave that death ensues in a few days.

A case reported by Elkin and Phillips [22] seems to have an important bearing on this question. In their first case, a stab wound severed the anterior descending branch of the left coronary artery and the accompanying vein. At the time the first electrocardiogram was taken (forty minutes after the patient was stabbed) the tracing was essentially normal. At this time, because of tamponade of the heart, the radial pulse was imperceptible and the blood pressure could not be determined. After the clot was evacuated from the pericardium, the heart began to beat more strongly and the pulse became perceptible at the wrists. At the end of the operation, the systolic blood pressure in millimeters of mercury was 90 and the diastolic 60. Ten minutes after that, the electrocardiogram began to show a rise of the R T segment in lead I and a depression of the S T segment in lead III. On the second day, the systolic blood pressure was 110, and it ranged between that level and 120 during the patient's stay in the hospital. The electrocardiogram

22. Elkin, D. C., and Phillips, H. S.: Stab Wound of the Heart: Electrocardiographic Studies of Two Cases, J. Thoracic Surg **1**:113 (Dec.) 1931.

taken thirty-six hours after operation showed classic R T deviations. It seems to me to be a fair assumption that the greatest degree of cardiac failure existed at the time the first tracing was taken. Evidence of some improvement in the function of the heart existed by the time the second tracing was taken, and at that time R T changes began to appear. But thirty-six hours after operation, when the blood pressure was approximately normal, the classic R T deviations were present. Certainly this result of an operation on a human being is not in keeping with the hypothesis that heart failure, in the presence of coronary occlusion, is the essential factor in producing the R T deviation.

The correlation of the site of infarction and the electrocardiographic changes was studied by two additional methods that permitted better localization of the site of infarction than was afforded by the ligation of vessels. Crawford, Roberts, Abramson and Cardwell [23] studied the effect of lesions produced by cautery in various portions of the wall of the two ventricles of the heart of the cat. They found that lesions of the anterior wall of the left ventricle produced tracings of the T_1 type, whereas those in the posterior wall of the left ventricle resulted in tracings of the T_3 type. Lesions produced in the right ventricle resulted in electrocardiograms of the T_3 type, except those located in the anterior basal portion of the right ventricle. After dividing the ventricles of the dog into similar zones and producing lesions in the various portions by the insertion of radon seeds, Haney, Borman and Meek [24] studied the electrocardiographic changes that occurred. They found that lesions of the anterior portion of the left ventricle produced electrocardiographic changes of the T_1 type, whereas lesions of the posterior portion of the left ventricle produced lesions of the T_3 type. The changes observed following injury to the right ventricle were more variable; in general, injury of the anterior portion of this ventricle produced a T_1 type of tracing, and a lesion on its posterior portion produced a T_3 type. These two groups of observers pointed out that, so far as the left ventricle was concerned, their results were in agreement with those of Barnes and Whitten in the localization of infarcts in the heart of man.

Fowler, Rathe and Smith [25] confirmed the observation previously made by Mann and me that injury to the pericardium is followed by successive changes in the T wave of the electrocardiogram. Fowler,

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23. Crawford, J. H.; Roberts, G. H.; Abramson, D. I., and Cardwell, J. C.: Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, Am. Heart J. **7**:627 (June) 1932.

24. Haney, H. F.; Borman, M. C., and Meek, W. J.: The Relation Between the Position of Experimental Myocardial Lesions in the Dog and the Changes in the RS-T Segment of the Electrocardiogram, Am. J. Physiol. **106**:64, 1933.

25. Fowler, W. M.; Rathe, H. W., and Smith, F. M.: The Electrocardiographic Changes Following the Ligation of the Small Branches of the Coronary Arteries, Am. Heart J. **8**:370 (Feb.) 1933.

Rathe and Smith pointed out that these changes are associated with demonstrable inflammation of the superficial muscle fibers subjacent to the region of pericarditis. They described the results of ligation of small branches of the coronary arteries, and they observed changes in the T wave that followed. It is not clear how they excluded the influence of pericardial injury on the electrocardiogram in this type of experiment. The electrocardiogram that they obtained (their fig. 1) following injury to the pericardium only does not differ materially from that produced by ligation of an anterior branch of the coronary artery (their fig. 1). They expressed the opinion that the change in the T wave following coronary occlusion is the primary event and that "the alterations in the R T segment are secondary to the latter manifestations." This conclusion is not in accord with the experience of other investigators. It certainly is not borne out by a study of electrocardiograms of acute myocardial infarction in man. Parkinson and Bedford pointed out that the R S-T segment frequently is displaced before a T wave is present or recognizable, and certainly before it is inverted, an observation which I have frequently confirmed.

Finally, Fowler, Rathe and Smith considered that closure of the smaller branches of the coronary arteries in man is often responsible for the anginal syndrome. They raised the question whether serial electrocardiograms may not be important in detecting these minor injuries to the myocardium. Clinically, I have been impressed with the number of patients suffering from severe coronary disease with marked symptoms of angina pectoris who showed no abnormality of the R S-T segment or of the T wave in the electrocardiogram. This has been true of patients under daily observation, when frequent electrocardiograms have been taken. Wood and his associates [26] observed significant electrocardiographic changes during attacks of angina pectoris, but these changes have been of such a transitory nature that it seems highly improbable that they had their genesis in the occlusion of a small coronary branch.

Although certain discrepancies appear among these observations, there is considerable agreement on the following points: 1. Injury of the pericardium without coronary ligation produces a remarkable series of changes in the form and direction of the T wave. 2. Although the injured region will fail to contribute its normal component to the electric field, the conventional leads may not detect this failure. This is particularly likely to be true of acute myocardial infarction produced by ligation of the anterior descending branch of the left coronary artery.

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26. Wood, F. C.; Wolferth, C. C., and Livezly, M. M.: Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion, Arch. Int. Med. **47**:339 (March) 1931.

3. It is essential in tapping the electric currents of the heart that the heart be surrounded by a suitable conducting medium. 4. Acute injury to the right as well as to the left ventricle in animals, whether produced by experimental coronary occlusion or otherwise, results in deviation of the R S-T segment. 5. Acute infarction in the anterior portion of the left ventricle in animals produces changes in the R S-T segment that differ characteristically from those that follow infarction of the posterior portion of the same ventricle. 6. At least two observations [27] agree that experimental infarction of the anterior portion of the left ventricle produces a T_1 type of electrocardiogram whereas infarction of the posterior portion of the same ventricle produces a T_3 pattern. The observers pointed out that their findings were in agreement with the electrocardiographic localization of infarcts in the left ventricle as described in the heart of man.[3]

CLINICAL ELECTROCARDIOGRAPHIC OBSERVATIONS

Pardee,[28] in 1920, first called attention to the electrocardiogram of acute coronary occlusion. He noted that the R S-T levels were disturbed and that the T waves were likely to be tall. He pictured the return of the R T level to normal and the sharp inversion in two leads. Subsequently,[29] he described the significant electrocardiographic feature of coronary occlusion, whether sudden or gradual, as "the presence in one or more leads, usually in only one, of a downward sharply peaked T wave with an upward convexity of the S-T or R-T interval" (fig. 3, *C, G*).

In 1928, Parkinson and Bedford [5b] reported a remarkable series of electrocardiographic tracings obtained following acute myocardial infarction. They found that the changes in the RS-T segment of the electrocardiogram fell into two groups, which they designated as T_1 and T_3 types. Whitten and I [30] had arrived at a similar conclusion and had accepted their nomenclature. The T_1 type of electrocardiogram (fig. 1 *A,B,C,D*; fig. 2 *A,B,C,D*) is characterized in its earliest development by a change of the level and contour of the RS-T segment in leads I and II and a depression of the S T interval in lead III. The R T interval in leads I and II, but especially in lead I, usually is elevated above the iso-electric line. The interval is likely to be convex, dome-shaped or sloping downward toward the T wave. Diphasic waves

27. Crawford, Roberts, Abramson and Cardwell.[23] Haney, Borman and Meek.[24]

28. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**:244 (Aug.) 1920.

29. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms with Special Reference to the Coronary T-Wave, Am. J. M. Sc. **169**:270, 1925.

30. Barnes, A. R.: Electrocardiographic Localization of Myocardial Infarcts, M. Clin. North America **14**:671 (Nov.) 1930. Barnes and Whitten.[18]

or T waves of a monophasic type are common in the earliest stages. It is important to note that leads I and III act conversely, so that the elevation of the R T segment in lead I is opposed by the depression of the S T segment in lead III. The changes in lead II, although less in degree, frequently are seen to be similar to those in lead I in cases of infarction in the anterior portion of the left ventricle. At a later stage the monophasic or diphasic type of T wave in lead I, or leads

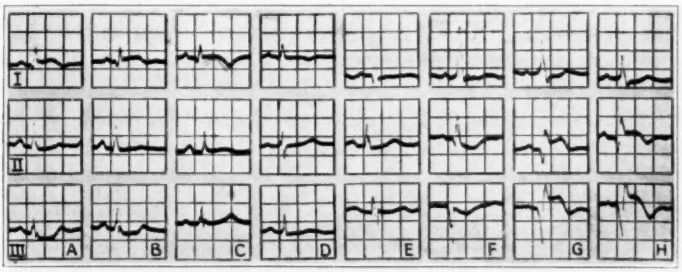

Fig. 1.—A Q_1 T_1 type of electrocardiogram, taken (*A*) one day, (*B*) three days, (*C*) twelve days and (*D*) twenty-eight days, after acute coronary occlusion, and a Q_3 T_3 type of electrocardiogram taken (*E*) two days before, (*F*) the day of, (*G*) the day following and (*H*) three days after, acute coronary occlusion.

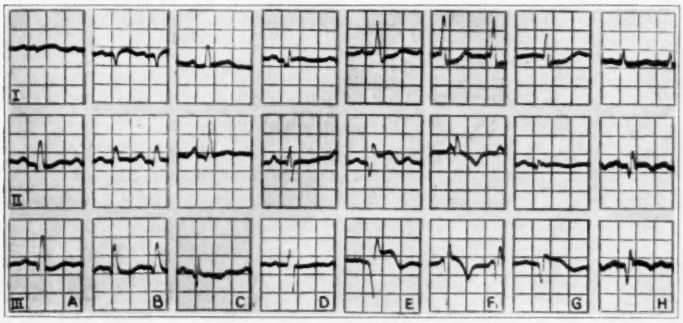

Fig. 2.—*A*, *B*, *C* and *D* show a T_1 type of electrocardiogram taken of four different patients during the first week after acute infarction of the anterior and apical portion of the left ventricle. *E*, *F*, *G* and *H* show a T_3 type of electrocardiogram taken of four different patients during the first week after acute infarction of the posterior basal portion of the left ventricle.

I and II, is replaced by frank inversion. It is worthy of note that as the T wave becomes inverted in lead I, the T wave in lead III remains upright and becomes exaggerated and sharply peaked (fig. 1*C*; fig. 3*C*). Of particular significance in the later stages is the fact that the R T segment arises at or only slightly above the iso-electric level and often

retains the rounded contour in lead I or in leads I and II, preceding the inverted T wave (fig. 3 *C,D*). Pitfalls of interpretation will be avoided if one does not interpret RS-T segments in lead I which arise below the iso-electric level as evidence of infarction. Conditions producing left ventricular strain are prone to produce a negative T wave in lead I with an S T segment arising below the iso-electric level (fig. 5 *A,B,C*) in the absence of myocardial infarction.[4]

The T_s pattern (fig. 1 *E,F,G,H*) is characterized by precisely the opposite type of RS-T changes following acute myocardial infarction. In its early stages the R T segments are elevated in leads II and III and the S T segment is depressed in lead I (fig. 1 *G,H*). A convex, dome-shaped or sloping R T segment preceding the T wave is observed in leads II and III. In the later stages the R T segment in leads II and III tends to return to, and eventually reaches, the iso-electric level,

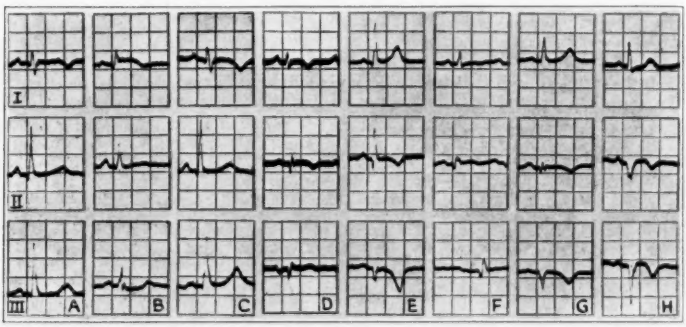

Fig. 3.—*A, B, C* and *D* show a T_1 type of electrocardiogram taken of four different patients from two to five weeks after acute coronary occlusion. *E, F, G* and *H* show a T_s type of electrocardiogram taken of four different patients from two to five weeks after acute coronary occlusion.

and the depressed S T segment in lead I disappears (fig. 2*H*; fig. 3 *E,G,H*). In this stage inversion of the T wave in leads II and III, with a rounded contour of the RS-T segment, is observed, whereas the T wave in lead I is upright and becomes exaggerated and sharply peaked (fig. 3 *E,G*). Here again one must insist in the later stages that the R T segment preceding the negative T waves in leads II and III arises on or above the iso-electric line, if the contours of the segments are to be regarded as evidence of a preceding acute myocardial infarction.

It is essential to the recognition of the electrocardiogram of acute myocardial infarction that one be familiar with these typical patterns. The feature of these patterns distinguishing them from all other electro-

cardiographic changes is the behavior of the RS-T segment in the first ten days after acute coronary occlusion. It is characterized by a reciprocal relation between the RS-T segments in leads I and III. When the R T segment is elevated in lead III (R T in lead II is usually simultaneously elevated), the S T segment in lead I is depressed. Conversely, when the R T segment is elevated in lead I, the S T segment in lead III is depressed (figs. 1 and 2). It has been contended that similar RS-T deviations are encountered in rheumatic fever,[31] in rheumatic carditis following roentgen therapy,[32] in pericardial effusion, under both clinical and experimental conditions,[33] in uremia [34] and in pneumonia.[4] Examination of the tracings submitted in these conditions reveals the fact that they lack the reciprocal relation of the RS-T segments in leads I and III. So far as I have been able to interpret reported tracings, the classic electrocardiogram of acute myocardial infarction is reproduced by no other pathologic process in the heart.

Valuable studies have been reported [35] that stressed the importance of progressive change in the electrocardiogram as evidence of acute coronary occlusion. Although that observation is important and valid, the closer these changes approach the classic electrocardiographic pattern of acute coronary occlusion, the more convincing they become as evidence of an acute closure of a coronary vessel. Progressive changes of the RS-T component are seen in the electrocardiograms of patients with acidosis of diabetes, of patients who have received digitalis, of patients under treatment for myxedema and of certain patients suffering from exophthalmic goiter treated with iodine and by partial resection of the

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31. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1 (Jan.) 1924. Rothschild, M. A.; Sacks, B., and Libman, E.: The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, Am. Heart J. **2**:356 (April) 1927.

32. Levy, R. L., and Golden, Ross: The Treatment of Rheumatic Carditis by Roentgen Irradiation of the Heart, Am. Heart. J. **4**:127 (Dec.) 1928.

33. (*a*) Katz, L. N.; Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion: II. Experimental, Am. Heart J. **5**:77 (Oct.) 1929. (*b*) Scott, R. W.; Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion: I. Clinical, ibid. **5**:68 (Oct.) 1929.

34. Wood, J. E., Jr., and White, P. D.: The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, Am. J. M. Sc. **169**:76, 1925.

35. (*a*) Cooksey, W. B., and Freund, H. A.: Serial Electrocardiographic Studies in Coronary Thrombosis, Am. Heart J. **6**:608 (Feb.) 1931. (*b*) Sigler, L. H.: Acute Coronary Occlusion. A Clinical and Electrocardiographic Study of Twenty Cases, Ann. Int. Med. **4**:969 (Feb.) 1931. (*c*) Wilson, F. N.; Barker, P. S.; Macleod, A. G., and Klostermeyer, L. L.: The Electrocardiogram in Coronary Thrombosis, Proc. Soc. Exper. Biol. & Med. **29**:1006 (May) 1932.

thyroid gland. These changes approximate no predictable pattern and hence are of no value in establishing or excluding the presence of acute coronary occlusion.

Aside from the classic RS-T changes just described, there is no other change in the T wave that indicates with certainty the presence of previous acute coronary occlusion. The T wave of coronary occlusion described by Pardee [29] is highly suggestive of acute coronary occlusion, but it has been closely simulated in cases of at least one other condition. However, whenever typical Pardee T waves are observed in lead I or leads I and II (fig. 3 *C,D*), or in the combined leads II and III (fig. 3 *E,G,H*), a diagnosis of a previous acute myocardial infarction can never be positively excluded until the heart is examined at necropsy.

Unfortunately, the typical pattern of electrocardiographic changes of acute coronary occlusion frequently is not observed following acute myocardial infarction. The reasons for this will be brought out in an analysis of the cases of acute myocardial infarction in which necropsy was done. In some instances, elevation of the R T segment was observed in lead I, in leads I and II (fig. 2*D*) or in leads II and III (fig. 2*H*), without a reciprocal depression in leads III and I, respectively. At times, especially in lead I, the R T segment never rises above the iso-electric line (fig. 2*A*), but there is a definite upward rounding of the segment preceding the shallow inversion of the T wave (fig. 4*A*). If a tracing taken before an attack clinically suggestive of acute coronary occlusion is normal so far as the R T segment is concerned, then this minimal change becomes highly significant. If further electrocardiograms disclose an increasing depth of the T wave and inversion and accentuation of the upward rounding of the preceding R T segment, the so-called Pardee wave, then such a development practically establishes the presence of acute myocardial infarction. The evidence is further strengthened if, as the depth of the inversion of the T wave in lead I increases, T_3 becomes taller and more abrupt.

Lacking these changes which approach a definite electrocardiographic pattern of acute myocardial infarction, the clinical impression will be supported, though not conclusively, by an electrocardiogram showing progressive changes. These changes include: the exaggeration of the T wave, followed by its depression or inversion; a change in voltage, usually consisting of a decrease; the appearance of a prolonged Q wave, especially significant in leads I and III; the appearance and disappearance of delay in conduction in either the auriculoventricular bundle or the bundle branches, and the occurrence of tachycardia paroxysmal in its onset and of auricular flutter or auricular fibrillation—any of which may occur during the course of an attack clinically suggestive of acute coronary occlusion.

Wilson and his associates [36] recently described certain changes in the initial deflections of the ventricular complex in association with myocardial infarction. They classified these changes under the headings of Q_1 and Q_3 types.

They found the Q_1 type to be characterized by "the presence of a conspicuous and, in most instances, rather broad Q wave in lead I; the absence of Q in leads II and III; the small amplitude of the largest of the initial deflections in lead I; and the presence of a conspicuous S in leads II and III" (fig. *2D*).

The Q_3 type is characterized by "the absence of Q in lead I, the presence of a conspicuous Q in leads II and III and the relatively small amplitude of the initial ventricular deflections in lead II" (fig. *2 E,F, G,H*).

In a recent study [37] of the correlation of the Q_1 and Q_3 types of electrocardiograms, with the site of myocardial infarction disclosed at necropsy, a definite localizing value was found. A typical Q_1 type of electrocardiogram is associated with acute or healing acute infarction in the anterior apical portion of the left ventricle and a typical Q_3 type with acute or healing infarction involving the posterior basal portion of the same ventricle. In another study [38] of the Q and T types of electrocardiographic changes following acute myocardial infarction, it was found that the two types of changes had important complementary value. At some stage after acute coronary occlusion, either type may exist as the sole evidence of acute myocardial infarction, or both may be present simultaneously, with one more typical than the other. Only by the combined consideration of the Q and T types of changes will one derive the greatest assistance from the electrocardiogram in making the diagnosis of acute coronary occlusion.

Electrocardiograms taken with thoracic leads recently have been reported [39] to give information about acute myocardial infarction in addition to that obtained with the standard electrocardiographic leads. Evidence is submitted [39] that in infarction presumably involving the anterior and apical portions of the left ventricle the deviation of the

36. Wilson, F. N.; Macleod, A. G.; Barker, P. S.; Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, Heart **16:** 155 (June) 1933. Wilson, Barker, Macleod and Klostermeyer.[35]

37. Barnes, A. R.: Correlation of Initial Deflections of Ventricular Complex of Acute Myocardial Infarction, Am. Heart J. **9:**728 (Aug.) 1934.

38. Barnes, A. R.: Q and T Types of Electrocardiograms: Their Comparative and Complementary Value in Indicating Occurrence of Acute Myocardial Infarction, Am. Heart J. **9:**722 (Aug.) 1934.

39. Wood, F. C.; Bellet, Samuel; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion; Further Observations on the Use of Chest Leads, Arch. Int. Med. **52:**752 (Nov.) 1933. Wood and Wolferth.[21]

RS-T segment is likely to be more pronounced and lasting in the thoracic leads than in the standard electrocardiographic leads. No doubt this fact will be borne out in infarctions so situated, following which the electrocardiographic evidence in the standard leads consists almost entirely of the appearance of an inverted T wave in lead I, with the RS-T segment arising on or only slightly above the iso-electric line. In acute infarctions presumably involving the posterior portion of the left ventricle, the thoracic leads were less diagnostic than the standard leads. In only one instance of infarction in such a location did the thoracic lead furnish convincing evidence not shown by the standard leads. These observations are important and will lead to widespread clinical utilization. However, in my experience, if one is familiar with the changes in the initial and final ventricular complexes of the standard leads that constitute or approximate the classic changes of acute myocardial infarction, and particularly if the features in both complexes are studied in conjunction, the use of thoracic leads is required only in the rarest instances to clinch the diagnosis of acute myocardial infarction.

Whitten and I [18] studied the localizing value of T_1 and T_3 types of electrocardiographic changes. We found that a T_1 type was associated with acute infarction of the anterior apical portion of the left ventricle and the T_3 type with acute infarction involving the posterior basal portion of the same ventricle.

A number of observers have reported cases confirming the fact that the electrocardiographic changes in the RS-T segment following acute myocardial infarction have definite localizing value.[40] Wolferth [41] stated that he had not seen any case in which the electrocardiogram could have been classified as one or the other of the groups described by Whitten and me in which the situation of the infarct was not in the region predicted by our tables.

On the other hand, Gilchrist and Ritchie, in a very thoughtful article, questioned the localizing value of the electrocardiographic changes following infarction and called attention to a number of factors capable of distorting the ventricular complexes and thus of confusing the electrocardiographic pattern of acute myocardial infarction. These observers selected from the literature ten cases of coronary thrombosis,

40. Bell, A., and Pardee, H. E. B.: Coronary Thrombosis: Report of Two Cases with Electrocardiographic Localization of the Thrombus in the Right or Left Coronary Arteries, J. A. M. A. **94**:1555 (May 17) 1930. Rose, W. J., and Myers, Frank: Electrocardiographic Diagnosis of the Artery Occluded in Cardiac Infarction, Proc. Soc. Exper. Biol. & Med. **27**:681 (April) 1930. Wilson; Barker, Macleod and Klostermeyer.[85c]

41. Wolferth, C. C.: Diseases of the Heart and Blood Vessels, Progrès méd. **3**:109 (Sept.) 1931.

with the electrocardiograms and data obtained at necropsy. Analysis fails to indicate that their cases are in disagreement with localization on the basis of T_1 and T_3 types of electrocardiograms. Bundle branch block was present in two cases, and so prevented the classification of these two cases. In two cases of infarct in the anterior wall of the left ventricle and in one of infarct in the posterior portion of the left ventricle the electrocardiograms conformed to the patterns described by Whitten and me. The electrocardiogram in case 25 of their series was taken eighteen hours before death ("premortal"). This electrocardiogram suggests a T_1 type, although it is not typical. The apex of the heart was thinned out, and microscopic examination of the region disclosed the presence of polymorphonuclear leukocytes and of small regions of necrosis suggestive of recent infarction. There was an ancient infarct in the left basal portion of the left ventricle. It seems likely that multiple infarcts were present in this case. In case 49 of their series, multiple infarctions were present. The exact relation of the recent septal infarct to the apex on the one hand, or to the posterior base of the left ventricle on the other, was not stated. In case 65 of their series, an infarct in the posterior basal portion of the left ventricle was present, and an elevated R T segment in leads I and II without S T depression in lead III is probably accounted for by acute fibrinous pericarditis [42] and the accumulation of 12 ounces (360 cc.) of blood-stained effusion in the pericardium. In case 98 of their series, a curve was obtained that was in no way typical of infarction. The history suggests the occurrence of multiple occlusions. The electrocardiogram was premortal, being taken on the day of death. In case 112 of their series, the electrocardiogram taken fifteen days after occlusion showed Pardee T waves of T_1 type. The infarction involved the apex and extended up over the posterior surface of the left ventricle. Acute apical infarction usually produces a T_1 type of electrocardiogram.

Similarly, one may analyze four cases reported by Burton and his associates.[43] In case 1 of their series, infarction in the posterior basal portion of the left ventricle with a T_3 type of electrocardiogram was present. In case 2, progressive congestive failure without a clinical history of angina pectoris or coronary thrombosis was present. Patchy fibrosis of the anterior part of the septum was found at necropsy. The electrocardiogram was not suggestive of infarction, and there was no

42. Barnes, A. R.: Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis; Report of Cases, Am. Heart. J. **9**:734 (Aug.) 1934.

43. Burton, J. A. G.; Cowan, John; Kay, J. H.; Marshall, A. J.; Rennie, J. K.; Ramage, J. H., and Teacher, J. H.: Four Cases of Fibrosis of the Myocardium with Electrocardiographic and Postmortem Examinations, Quart. J. Med. **23**:293 (April) 1930.

reason to expect that it would be, as the infarct presumably was of the chronic dystrophic type. In case 3, multiple regions of chonic fibrosis were present, one of which probably represented an ancient healed acute infarction and the others, areas of chronic dystrophic fibrosis. The electrocardiogram could not be expected to show changes, probably because it was taken too long after acute infarction had occurred. In case 4, there was no history of occlusion, but the first electrocardiogram is distinctly suggestive of subacute infarction in the anterior apical portion of the left ventricle. At necropsy, four months later, a healed acute infarct in this area was found. The two subsequent electrocardiograms, without evidence of myocardial infarction, simply represent the return to normal with healing of the acute infarct. These are not specious explanations of apparent discrepancies; they are explanations based on a knowledge of various factors which experiment and observation have led me to believe is correct.

In order to test the validity of the electrocardiographic criteria for determining the presence and site of acute myocardial infarction, I am reviewing all the cases of this type which have been seen at the Mayo Clinic in the past six years.

DATA ON ONE HUNDRED AND FIVE CASES OF MYOCARDIAL INFARCTION PROVED AT NECROPSY

These cases of infarction were classified in three categories:

1. In the first category are fifty cases in which occlusion of a coronary vessel or acute myocardial infarction was discovered at necropsy. In seventeen the electrocardiographic findings accurately indicated the presence and site of the acute myocardial infarct or infarcts. In four of these cases the electrocardiograms were indicative of an infarction of the anterior and apical portion of the left ventricle, the location being confirmed at necropsy. In eleven of the seventeen cases, the electrocardiograms were characteristic of infarction in the posterior basal portion of the left ventricle, with confirmation at necropsy. In two of the seventeen, acute infarctions of both the anterior apical and the posterior basal portion of the left ventricle existed, and a sufficient interval elapsed between these infarctions that the electrocardiogram could localize the infarctions in each portion. Reports of these two cases have been published previously (cases 2 [30] and 3 [18]).

In thirty-three cases, electrocardiographic evidence of myocardial infarction was not obtained; in eighteen no electrocardiographic tracing was obtained after the occurrence of acute coronary occlusion; in two bundle branch block occurred, preventing the appearance of the electrocardiographic changes of acute occlusion, and there were twelve instances in which multiple acute infarctions occurred. It has been

my associates' and my experience at the clinic that multiple infarctions, particularly if the anterior apical and posterior basal portions of the left ventricle are simultaneously involved, prevent the appearance of the typical electrocardiographic signs of occlusion. This can be readily understood when one recalls that these two regions have opposing effects on the changes in the RS-T segment of the electrocardiogram. Therefore, the simultaneous involvement of these two areas produces mutually antagonistic effects which more or less completely neutralize the total effect on the RS-T segment. In one case in which acute coronary occlusion was complicated by acute pericarditis, elevation of the RS-T segment occurred in all leads, followed later by negativity of the T wave in all derivations (fig. 6 *A,B,C,D,E*). A series of cases with this type of electrocardiographic change has been studied, and evidence has been submitted that this peculiar modification of the usual RS-T pattern may occur when acute coronary occlusion is complicated by pericarditis.[42]

2. In a second category of twenty-nine cases, necropsy revealed infarction which was classified as healed acute infarction. It is not always possible to distinguish this from the third type, classified as chronic dystrophic fibrosis. However, I have classified the second type as healed acute infarction when there was definite ancient occlusion of a vessel above the site of localized fibrosis, for example: (*a*) when a localized fibrous replacement of the muscle resulted in aneurysmal dilatation; (*b*) when ancient pericarditis overlay an area of localized fibrosis of the myocardium, and (*c*) when a well organized thrombus underlay a region of more or less localized fibrous replacement of the myocardium. No history of acute coronary occlusion was obtained in sixteen of these twenty-nine cases, although that does not mean that such a history might not have been obtained in some by rigorous interrogation. Of the remaining cases, in all but three the history indicated that coronary occlusion occurred one year or more before the electrocardiogram was taken; in these three, occlusion occurred nine, five and two months, respectively, before the tracing was taken. There were two electrocardiograms in which relics of an acute occlusion were indicated, and in each instance the electrocardiograms accurately revealed the situation of the infarct. The remaining electrocardiograms gave no clue as to the previous occurrence of acute myocardial infarction. This probably can be accounted for by the fact that almost all the tracings were taken too long after acute occlusion had occurred.

3. Such cases of chronic myocardial infarction as did not fulfil the conditions imposed for inclusion in the second type were classified as instances of chronic dystrophic fibrosis. The third category comprised twenty-six cases. Complete or incomplete bundle branch block occurred

in six cases. The electrocardiogram in one case showed auricular flutter, and that in another, auricular fibrillation. The electrocardiograms in two cases were indeterminate because of poor tracings. In one case, low voltage of the Q R S complex and T wave in all leads was indicated. In one case, the tracing showed an upward rounded S T segment in lead III, with a depressed S T segment in lead I. The infarction was incidental to extensive pathologic changes in the heart, consisting of subacute bacterial endocarditis superimposed on chronic rheumatic and aortic endocarditis with calcareous stenosis of the aortic valve. In nine cases, abnormal T waves were found in lead I or in leads I and II. It has been pointed out previously that if hypertension produces abnormal T waves, the abnormalities occur in those leads. It should be pointed out here, too, that the S T segment in hypertension is likely to have a certain pattern which is characterized chiefly by a depressed S T level in lead I or in leads I and II in conjunction with negative T waves in those leads. Such a change in the S T level must be distinguished sharply from the elevations of the RS-T segment suggesting acute infarction (fig. 5 *A,B,C*). Finally, the tracings in five cases classified as instances of chronic dystrophic fibrosis were normal. It is the fashion when any type of RS-T change is observed in angina pectoris or coronary sclerosis to attribute that change invariably to coronary disease. Such a practice is unscientific and clinically unsound. Every clinician knows that there are numerous cases of angina pectoris and coronary sclerosis with or without chronic dystrophic changes in the myocardium in which the electrocardiograms are normal.

It is proved beyond doubt that acute coronary occlusion can produce modifications of the RS-T segment of the electrocardiogram. When coronary sclerosis produces delay in the conduction of the bundle branches, abnormal RS-T changes usually result. Definite transitory changes in the RS-T segments have been observed in some cases in which electrocardiograms were obtained during attacks of angina pectoris. But apart from these mechanisms, it has never been proved that coronary sclerosis, of itself, or even chronic dystrophic myofibrosis, can be held to account for modifications of the RS-T segment or of the T waves of the electrocardiogram. For this reason the "coronary T wave" should be designated the "coronary occlusion T wave." In the presence of angina pectoris and coronary sclerosis, other independent factors may be present and modify the RS-T segment and the T waves. Such factors are: predominant ventricular strain,[44] most commonly due to hypertension; pericarditis or sudden pericardial effusion; myocarditis; toxic factors, particularly the results of digitalis therapy, and metabolic disorders, especially diabetic acidosis and myxedema. The

44. Barnes, A. R., and Whitten, M. D.: Study of T-Wave Negativity in Predominant Ventricular Strain, Am. Heart J. **5**:14 (Oct.) 1929.

presence of a great percentage of normal RS-T components in the electrocardiograms in cases of advanced coronary disease need assure no one of the absence of such a disorder, and, conversely, the presence of RS-T changes, except for the definite pattern seen following acute coronary occlusion, need lead no one to the easy conclusion that such changes necessarily are to be attributed to the presence of coronary sclerosis.

DATA ON ONE HUNDRED AND THREE CASES WITH A CLINICAL HISTORY OF ACUTE CORONARY OCCLUSION NOT CONFIRMED AT NECROPSY

It must be admitted at the outset that the electrocardiogram of acute myocardial infarction, no matter how pathognomonic it is in the beginning, loses its absolute diagnostic value in from two to four weeks

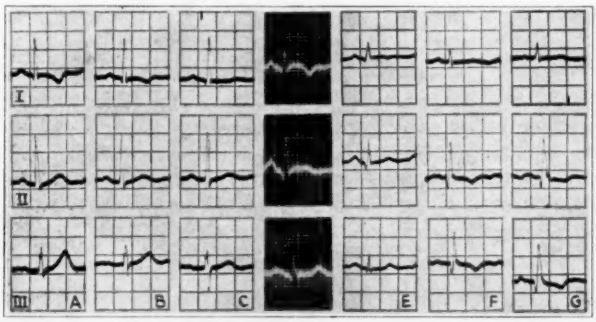

Fig. 4.—Electrocardiograms showing residual changes of the T_1 type taken (*A*) five weeks, (*B*) eleven weeks, (*C*) thirty-one weeks, (*D*) five weeks, and (*E*) three years and nine months, after acute coronary occlusion. Each tracing represents a separate patient, and typical electrocardiograms of a T_1 type had been obtained of each patient in the first week after acute coronary occlusion. Tracings *F* and *G* were taken of a patient three months and three years and three months, respectively, after acute coronary occlusion. A tracing taken of this patient seven days after occlusion was typical of the T_3 type.

after acute coronary occlusion. After that time, however, it may retain features highly suggestive of previous acute myocardial infarction in the form of Pardee's "coronary T waves." These waves are characterized by the origin of the R T segment on or slightly above the iso-electric level and the upward rounding of the R T segment and its termination in a sharp, deep T wave. Such waves, after acute infarction involving the anterior apical portion of the left ventricle, are seen in lead I or, rarely, in leads I and II (fig. 4 *A,B,D*). When the acute infarction involves the posterior basal portion of the left ventricle, the R T segments of leads II and III take on the peculiar character described

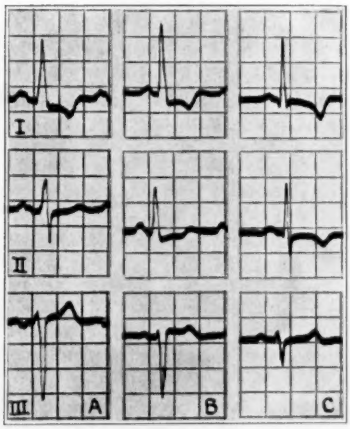

Fig. 5.—*A, B* and *C* show electrocardiograms taken of three patients who had marked essential hypertension but without coronary occlusion or myocardial infarction. The depressed S T segment in association with the negative T waves in the first lead may be contrasted with the iso-electric or slightly elevated RS-T segment of electrocardiograms of the T_1 type obtained as a late relic of acute coronary occlusion.

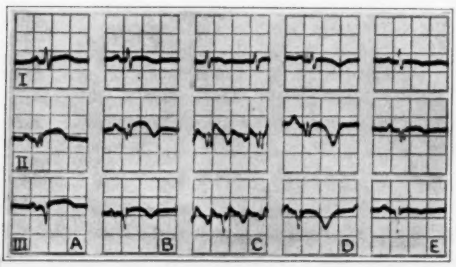

Fig. 6.—Electrocardiograms taken in a case of acute coronary occlusion complicated by pericarditis, taken (*A*) two days, (*B*) six days, (*C*) eight days, (*D*) twenty-one days and (*E*) four months, after the onset of the attack. Necropsy gave evidence of occlusion of the anterior descending branch of the left coronary artery with extensive healed acute infarction of the anterior and apical portion of the left ventricle. There was extensive chronic adherent pericarditis overlying the area of infarction.

by Pardee.[29] Commonly, as T_1 becomes deeply inverted, T_3 becomes upright, sharp and exaggerated, and the same happens to T_1 as the T waves in leads II and III become deeply inverted. Finally, shallow inversions of the T wave in lead I (fig. 4*E*) or in the combined leads II and III (fig. 4 *F,G*), if the preceding R T segment has remained isoelectric or slightly elevated, are often the last positive electrocardiographic evidence of relics of a previous acute infarction (fig. 5).

Most of these patients recovered; those who died did not come to necropsy. Only thirteen were seen within the first week after the acute occlusion.

In only four of the one hundred and three cases were the electrocardiograms normal. In these four cases tracings were taken three and a half, five, twelve and eighteen months, respectively, after acute occlusion. In thirty-one cases tracings conforming more or less closely to a late type I pattern were found; in eight of these there were definite Q waves in lead I. In thirty-four cases electrocardiograms belonging to a late type 3 pattern were found; in thirty of these there were prolonged Q waves in lead III, and both T_1 and T_3 types of electrocardiograms were observed in four cases in which multiple acute occlusions occurred. Bundle branch and auriculoventricular block and auricular fibrillation and flutter comprised the electrocardiographic changes encountered in twenty-nine cases. In only one case in the entire group in which frequent electrocardiograms were taken in the first three weeks after an attack clinically characteristic of acute occlusion did an electrocardiographic pattern characteristic of acute myocardial infarction fail to develop. The pattern in this case did change, however, in that the T wave in lead III became negative, and a prolonged Q wave in lead III made its appearance. Definite pericarditis occurred in this case. The patient recovered, so that multiple occlusions could not be excluded from the diagnosis, and absolute proof that infarction had occurred could not be obtained.

The failures of the electrocardiogram to signalize myocardial infarction by changes in the RS-T segment were found to be explained by one of the following causes: 1. Electrocardiograms were not obtained in sufficient number or in the proper time relation to the occurrence of acute myocardial infarction. 2. There were multiple areas of acute myocardial infarction in the left ventricle. 3. The presence of bundle branch block obscured the electrocardiographic pattern of infarction. 4. Pericarditis or pericardial effusion modified the electrocardiographic changes. 5. The amplitude of the deflections in lead I or lead II was so small that the RS-T changes characteristic of infarction could not be recognized. 6. The tracing was taken of a patient who was dying.

In the attempt to corroborate or refute evidence of relation between the T_1 and T_3 types of tracings and the situation of the infarct

in the heart, careful anatomic study of the heart must be made. The situation and size of the infarct should be recorded as accurately as possible. Search for multiple infarcts should be made, and if more than one is present they should be studied and described so as to establish their relative age, if they differ in that respect. A careful attempt to distinguish chronic dystrophic fibrosis from a healed acute infarction should be made according to the criteria laid down earlier in this article. The investigation of the myocardium must include microscopic as well as macroscopic study. In the average pathologic study of the heart, the anterior portion of the heart receives minute attention but the posterior basal portion is not studied as carefully. The presence of a large healed infarct in the anterior portion of the heart may lead the examiner to overlook a less obvious, but more recent, infarct in the posterior base of the left ventricle; this happened in a case recently reported [36] and led to serious question of the hypothesis of localization. Moreover, it must always be borne in mind that the more recent infarct dominates the RS-T changes in the electrocardiogram. Finally, in my experience, the electrocardiogram, by changes in the RS-T segment or T wave, apart from defects of conduction in the bundle branches, does not reflect the presence of chronic dystrophic fibrosis as it is defined in this paper, and therefore this type of fibrosis cannot be localized by any type of electrocardiographic changes described to date.

It is of interest to consider how soon after occlusion electrocardiographic changes indicative of occlusion may develop. The opportunity to obtain tracings within a few hours after occlusion is seldom afforded. In three of our cases in which acute infarction was proved at necropsy, electrocardiographic evidences of acute occlusion were observed within twelve hours. In four cases with clinical evidence of coronary occlusion but without proof at necropsy of acute myocardial infarction, the electrocardiographic pattern of infarction occurred within twenty-four hours. Cooksey and Freund recorded changes at one, two and three hours after acute occlusion, and Bell and Pardee published a report of a case with changes in six hours. Elkin and Phillips' patient showed early electrocardiographic changes of acute occlusion approximately ninety minutes after the severance of the anterior descending branch by stabbing. In our experiments with dogs [19] marked characteristic electrocardiographic changes were observed from twenty to thirty minutes after ligation of a coronary vessel. Wood and Wolferth [21] observed changes in the RS-T segment two minutes after clamping a coronary vessel in the dog. Thus it is apparent that electrocardiographic changes characteristic of infarction may occur in a few hours after acute coronary occlusion. In those cases in which the changes appear more slowly, one suspects that occlusion took some time to

become complete or that the collateral circulation was sufficient to prevent a complete loss of anatomic and functional integrity of the muscle fibers in the area of infarction from occurring for some time. Certainly, tracings must be taken throughout the first week after acute occlusion before one concludes that the electrocardiogram of acute infarction failed to appear.

On the other hand, electrocardiographic changes of acute myocardial infarction may persist for a long time (fig. 4). In some of our cases the electrocardiogram showed a return to normal in three months, and in others it showed traces of the original abnormality for three years or more (figs. 4 *E* and *G*).

In a review of the literature as well as in a consideration of the cases forming the basis of this study, it was found that T_1 and T_3 types of electrocardiograms are about equally distributed in the cases in which recovery was made. The same is true of cases in which the patients died. Typical T_1 or T_3 types of electrocardiograms were encountered six times as often as atypical types in cases in which recovery was made. In the cases in which the patients died, atypical tracings of acute myocardial infarction predominated over typical tracings in a ratio of 4:3. This indicates that in the cases in which electrocardiograms after acute coronary occlusion show the closest approximation to the classic T_1 or T_3 pattern there is the best chance of recovery from the immediate attack. The atypical tracings frequently were found to be associated with multiple infarcts, with extensive single infarctions overrunning the localized regions of the heart, which yield the most characteristic electrocardiographic changes, or with infarctions complicated by pericarditis. This explanation derives support from some similar conclusions reached by Padilla and Cossio.[45] Low voltage of the Q R S complex in all leads was encountered twice as often in cases in which the patients died of coronary occlusion as it was in cases in which the patients recovered. Its presence, therefore, appears to increase the gravity of the prognosis.

CONCLUSIONS

1. A knowledge of the coronary blood supply of the left ventricle is essential to an understanding of the problem of acute coronary occlusion.

2. It is essential to bear in mind that acute infarction involving the posterior basal portion of the left ventricle is approximately as common as is infarction of the anterior apical portion of that ventricle.

3. It is the situation of the acute infarct in the left ventricle and not the vessel supplying the area that determines the character of the electrocardiographic changes that will result.

45. Padilla, T., and Cossio, P.: El electrocardiograma ventricular en el infarto miocardico, Semana méd. **36**:813, 1929.

4. Experimental ligation of vessels to the right and left ventricles of the dog produces electrocardiographic evidences of myocardial infarction that differ distinctly. Destruction of areas in the anterior portion of the left ventricle of the cat and of the dog produces electrocardiographic changes that are quite different from those obtained by the injury of similar portions of the posterior portion of the heart.

5. The characteristic feature of these electrocardiographic changes is a deviation of the RS-T segment.

6. Care must be exercised in interpreting the results of experimental ligation of coronary vessels to distinguish between the changes in the electrocardiogram produced by the pericardial reaction and those attributable to actual infarction of the myocardium.

7. The preponderance of evidence is against the interpretation that deviation of the RS-T segment in acute myocardial infarction depends on the development of an additional factor of cardiac failure.

8. Experimental and clinical evidence indicates that the RS-T deviation observed in the electrocardiogram after infarction is the primary event and that T wave changes are sequential and secondary to that deviation.

9. There is a definite pattern of RS-T changes characteristic of infarction in the anterior apical portion of the left ventricle and another indicative of infarction in the posterior basal portion of the left ventricle in the heart of man.

10. Although a constantly changing electrocardiogram observed after what is presumed to be acute coronary occlusion may be important corroborative evidence of that event, the degree with which these electrocardiographic changes approximate the T_1 or T_3 pattern will largely determine their worth in establishing the diagnosis of acute coronary occlusion.

11. Typically developed Q_1 and Q_3 patterns of infarction have a definite diagnostic and localizing value, and the combined consideration of the Q and T patterns will yield more information in the diagnosis than will either pattern considered alone.

12. Under proper conditions, the presence and situation of acute infarction can be predicted almost always from the electrocardiographic changes that develop. When changes in the electrocardiogram characteristic of acute myocardial infarction fail to develop, it will be found usually that tracings were not obtained in sufficient number or in proper time relation to the acute occlusion, multiple acute infarctions of the left ventricle were present, bundle branch block obscured the changes, pericarditis or pericardial effusion modified the electrocardiographic changes or the tracing was made at about the time of death.

13. Presumptive evidence of previous occlusion may be obtained from the appearance of inverted T waves observed months after the acute occlusion. These T waves are the coronary T waves of Pardee, and are chiefly characterized by their depth and the character of the R T intervals that precede them. The reciprocal relation of T_1 and T_3, in which as one becomes more inverted the other becomes more positive, is important evidence of preceding acute occlusion.

14. By no means are all RS-T changes observed in angina pectoris, coronary sclerosis or myocardial fibrosis to be ascribed to coronary disease.

15. Many cases of angina pectoris, coronary sclerosis and myocardial fibrosis present no significant electrocardiographic changes.

16. Neither the presence nor the situation of chronic dystrophic fibrosis of the myocardium is disclosed by any electrocardiographic change described to date.

17. Electrocardiograms with low voltage of the Q R S complex in all leads after acute infarction probably increase the gravity of the prognosis.

18. The development of highly characteristic electrocardiograms of the T_1 or T_3 type after acute infarction seems to indicate a more favorable prognosis than do atypical electrocardiograms.

19. Electrocardiographic changes signifying acute infarction may appear as early as from one to two hours after acute coronary occlusion, and the electrocardiogram may not return completely to normal in some instances for two or three years or more.

CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS

I. CLINICAL EVALUATION OF STUDIES OF CIRCULATING BLOOD VOLUME

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The importance of a determination of blood volume in clinical medicine has long passed the experimental stage. Sufficient work has been done to prove that an abnormal blood volume will sometimes throw light on the underlying cause of a disease, and that it is helpful in the differential diagnosis of such diseases as hyperthyroidism, polycythaemia vera and cardiovascular disease, constituting a valuable aid in prognosis and treatment.

Some clinicians, however, still deny the importance of studies of blood volume on the ground that there is no accurate method of determining the circulating blood volume. It is admitted that from the exact physiologic standpoint, the methods utilized are not absolute; but, on the basis of an immense amount of work by others and our own observations in a large series of cases, we are firmly convinced that the results obtained justify the application of studies of blood volume to clinical medicine.

Our series comprised seventy-three subjects: ten normal persons, nine with hyperthyroidism, twenty-two with cardiovascular disease, five with compensated hypertension, seven with polycythaemia vera, six with anemia (varied), seven with metabolic disorders, one with avitaminosis (scurvy) and six with neurocirculatory asthenia.

GENERAL TERMINOLOGY

Normally, the heart pumps out a certain amount of blood per unit of time from the ventricle into the periphery. This is known as cardiac output, minute volume or circulatory volume and is expressed in terms of liters per minute. The amount of blood ejected by the left ventricle with each systole is referred to as cardiac stroke, systolic output or

From the medical service of Dr. Marcus A. Rothschild, and the Laboratory Department of Beth Israel Hospital.

stroke volume and is the result of the cardiac output divided by the cardiac rate. The amount of oxygen given up by a unit volume of blood to the tissues is known as the arteriovenous oxygen difference and is expressed in cubic centimeters of oxygen per liter of blood. This gives a measure of the relative activities of the circulatory and metabolic functions. The arteriovenous oxygen difference divided by the total oxygen content of the arterial blood gives oxygen utilization expressed in terms of percentage.

The amount of blood present in the organism is known as the total blood volume. This must be differentiated into two types. The part of the blood passing the heart once in the circulation is known as the circulating, active or rapid blood volume. The part moving slowly or passively, as through the liver, spleen, splanchnic areas or subpapillary plexus, is known as the stagnant or passive blood volume. Clinically, when the term blood volume is used, it generally refers to the circulating or active type.

Circulatory time is the shortest time that it takes a particle of blood or a foreign body to traverse the circulatory system from the peripheral veins through the heart and out to the other peripheral vessels. Venous pressure is the pressure residue in the vascular system after the resistance in the peripheral vessels (arterioles, capillaries and venules) is overcome.

BLOOD DEPOTS

Spleen.—Whereas it is true that the various parts of the body that are called on to do the most active work need an additional supply of blood, this is not furnished by an increased frequency of rate or blood pressure, as was once thought, but by an increased stroke volume and cardiac output. The question that arises, then, is what is the source of the increase in circulating blood? The bone marrow does not produce red blood cells instantaneously nor can the tissues furnish the necessary fluid. Hence the increased supply of blood must come from certain areas where it is stored pending the time of need. In other words, there must exist in the body blood depots that are in readiness to supply blood to the tissues whenever this is necessary.

By blood depot is meant, to use Rein's [1] definition, an organ that is able to take up blood without affecting the nutritive or other needs of the concerned organ and without depriving the tissues of the body in general of their nutrition.

The existence of blood depots in the body was long suspected by physiologists, but there was no scientific demonstration of their exis-

1. Rein, H.: Die Blutreservoire des Menschen: Physiologie, Klin. Wchnschr. **12**:1 (Jan. 7) 1933.

tence until the ingenious studies of Barcroft [2] and his associates made this possible. Barcroft noticed that there is a variation in the circulating blood when a person ascends mountains or passes through warm regions near the equator or through excessively cold zones. This so impressed him and his associates that they concluded that temperature must be an influential factor in the circulating blood volume. Carrying this theory into physiologic experiment, they compelled rats to inhale carbon monoxide and found that the gas quickly saturated the arterial blood of the rats, and that, if the animal was killed at the height of the poison, the splenic venous blood was free of the gas. They explained this phenomenon by the fact that the blood of the spleen is not in direct contact with the blood in the rest of the circulatory system. If the rats were permitted to run about while inhaling the carbon monoxide, the blood in the splenic vein was found to contain carbon monoxide, proving that during exercise the splenic blood participates in the general circulation. In short, the spleen is a blood depot, possessing the property of active muscular contraction, as well as expansion, so that it can expel into the circulation the blood that it hoards in its diverticulum-like spaces. In man, however, the musculature of the spleen is much less than that of the spleen of animals (dog), and so it is doubtful if contractility of this musculature is the sole factor in the unloading of hoarded blood from the spleen into the circulation. An additional, and probably far more important factor, would seem to be the influence of the vegetative nervous system on the spleen, as shown by the fact that stimulation of the vagus system (by means of the injection of choline) causes the spleen to hoard blood, whereas stimulation of the sympathetic system (by the injection of epinephrine) causes the spleen to contract and expel its noncirculating (hoarded) blood into the circulatory system.

Liver.—For some time, Barcroft and others thought that the spleen was the only blood-hoarding organ. Then it was noticed that after splenectomy there continues to be a variation in the blood volume during work and at rest, so that it was apparent that the body must have blood depots other than the spleen. Naturally attention was first directed to the liver, and experiments were successfully carried out to prove that the liver is a blood depot.

Rein demonstrated the vascularization of the liver by measuring, with the Stromuhr, the inflow through the portal vein and hepatic arteries and the outflow through the inferior and superior vena cava. He also showed that the liver can retain a large amount of blood and deliver it to the circulation in time of need without physiologic dis-

2. Barcroft, J.: J. Physiol. **73**:344, 1931.

turbance. The blood of the liver constitutes 59 per cent of the weight of the blood-free organ, and of this, 39 per cent is active circulating blood and 20 per cent hoarded blood.

Several theories have been offered to explain the way in which the liver acts as a blood depot. Rein claimed that the expulsion of blood from it is a passive process, brought about by capillary dilatation and oozing. Dale and his associates [3] agree that emptying is a passive process (that is, not produced by the action of its smooth musculature), but differed from Rein by stating that the organ empties by paralysis rather than dilatation of the capillaries. Barcroft agreed that unloading is a passive action, but contended that it takes place by a change of capacity of the blood stream and is dependent on the capacity of the blood stream to dilate and contract. Mautner and Pick,[4] conversely, claimed that the hepatic veins have a musculature, with contractile and dilation properties, and that it is the contraction and expansion of this musculature which causes closure of the central veins (*Venensperre*) sufficient to retain the blood that is to be hoarded and expansion thereof to discharge the hoarded blood in time of need. Pick and Mautner showed that along the length of the branches of the central vein there is hypertrophy of the muscular walls which, under certain conditions, causes throttling (*Grosseln*) of the blood from the liver. These traction-like spaces which appear as small, converging vessels, form no closed mantle or covering, and can feed each other by acting as bolsters, increasing in width. In the liver of man and carnivorous animals, such an arrangement of the musculature is to be seen in the region of the convergence of the smaller veins into the larger ones.

Subpapillary Plexus of the Skin.—Wollheim [5] showed that the subpapillary network, which is spaciously situated between the end-capillaries and the subcutaneous tissue, can hoard as much as 1,800 cc. of blood, or 30 per cent of the total circulating blood. This has been confirmed by Barcroft and others. The blood of the subpapillary plexus is not derived from the general circulation by a shunting process, as in the case of the spleen, but by a blockage process, a large quantity of blood being absorbed from the circulation through small apertures. When filled, the subpapillary plexus contains slowly moving, stagnating blood, in contrast to the quick-flowing blood of the end-capillaries.

3. Bauer, W.; Dale, H. H.; Poulson, L. T., and Richards, D. W.: J. Physiol. **74**:343, 1932.

4. Mautner, H., and Pick, E. P.: Arch. f. exper. Path. u. Pharmakol. **97**:350, 1923.

5. Wollheim, Ernst: Die zirkulierende Blutmenge und ihre Bedeutung für Kompensation und Dekompensation des Kreislaufs, Ztschr. f. klin. Med. **116**:269 (April) 1931.

Lungs.—Hochrein and Keller [6] supported the theory that the lungs are a blood depot equal in importance to the spleen and liver. Rein, however, did not consider the lungs a real depot, but contended that the blood deposited there is the result of an alteration in the capacity of the blood stream. Change in capacity, he believed, is not identical with function as a depot. He admitted that there may be retention and expulsion of blood in the lungs owing to cardiac influence, but considered this different from hoarding. We agree with Hochrein and Keller that the lungs are hoarders of blood, though of less significance in this respect than the liver and spleen.

Large Veins.—Whether or not the large veins hoard blood is still a matter of discussion. Gollwitzer-Meier [7] and Henderson and Harvey [8] expressed the belief that the large veins have a mechanism for hoarding blood and that it is one of musculature. Elias [9] studied the function of the musculature of the large veins in man by means of heat, cold and electric stimulation and showed that there is a marked narrowing of the musculature of the veins where the hepatic vein converges into the inferior vena cava. We are inclined to believe that the large veins do not play much part, if any, in the hoarding of blood.

METHODS AND TECHNIC

Although it has been possible to determine experimentally in animals during life the amount of blood hoarded by the various blood depots, it has obviously been impossible to determine this clinically in man. Attempts to determine the circulating blood volume in man as well as in animals have been successful, however. For this purpose various methods and technics have been devised, ranging from the direct method of bleeding animals and decapitation, as advocated by Welcker [10] in 1854, to the intravenous injection of physiologic solution of sodium chloride with ammonium oxalate, as advocated by Plesch,[11] in 1919. Gréhant and Quinquaud,[12] in 1882, were the first to utilize carbon monoxide for determination of blood volume, and Kottman [13] was the first (in 1906) to try the intravenous injection of a foreign dye for determination of blood volume, using sodium indigotin disulphonate, U. S. P. (indigocarmine), and methylene blue.

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6. Hochrein, M., and Keller, J.: Arch. f. exper. Path. u. Pharmakol. **164**: 529; **166**:229, 1932.

7. Gollwitzer-Meier, K.: Venensystem und Kreislaufregulierung, Arch. f. d. ges. Physiol. **229**:264, 1931.

8. Henderson, Yandell, and Harvey, S. C.: VIII. The Venopressor Mechanism, Am. J. Physiol. **46**:353 (Aug.) 1918.

9. Elias, quoted by Eppinger.[21]

10. Welcker, H.: Blutkörperchenzählung und farbeprüfende Methode, Vrtljschr. f. d. prakt. Heilk. **54**:11, 1854.

11. Plesch, J.: Haemodynamische Studien, Ztschr. f. exper. Path. u. Therap. **6**:380, 1909.

12. Gréhant, N., and Quinquaud, E.: J. de l'anat. et physiol. **18**:564, 1882.

13. Kottman: Arch. f. exper. Path. u. Pharmakol. **54**:356, 1906.

It was not until 1915 that Keith, Rowntree and Geraghty [14] used colloidal dyes for the determination of the plasma and blood volume and established a method which, with various minor modifications, is now universally employed. By their method, a known amount of a nontoxic, slowly absorbable dye is introduced into the circulation to remain in the plasma long enough to become thoroughly mixed with it. The concentration of the dye in the plasma is determined colorimetrically by comparison with a suitable standard mixture of dye and serum, and the total circulating blood volume is computed by utilizing the hematocrit values.

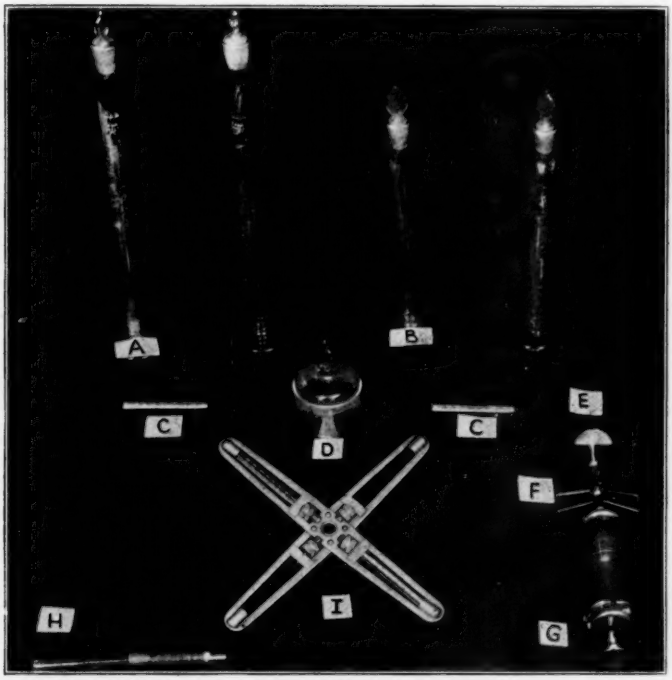

Fig. 1.—Apparatus used for determination of blood volume. *A* is a 15 cc. graduate collecting tube; *B*, a 10 cc. graduate collecting tube; *C*, hematocrit tubes; *D*, weight glass; *E*, cannula; *F*, Strauss connectors; *G*, 10 cc. syringe; *H*, venous pressure tubing with adapter, and *I*, centrifuge holder for hematocrit tubes.

We have employed this method, with certain modifications, as follows:

The blood of the patient was taken either five or six hours after a light breakfast or after no breakfast, with the patient in a recumbent position for at least half an hour before the test. All material was sterilized before being utilized. A

14. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547, 1915.

large special cannula with a Strauss connection was employed for the withdrawal of blood into measured cylinders. As soon as the blood began to flow from the median basilic vein, the tourniquet was removed, and the hand was held open. No unnecessary pressure was exerted while blood was flowing. Two specimens of blood (15 cc. each) were collected in this manner, to be utilized in making up a fresh standard for comparison (fig. 1).

A solution of 10 cc. of 0.6 per cent trypan red dye [15] was then injected into the patient's vein at body temperature, care being taken to wash away any of the dye remaining on the wall of the vein by pushing the piston of the syringe back and forth twice. Using a stop-watch, three minutes after the injection of the trypan red dye 10 cc. of blood mixed with dye was withdrawn, and three minutes later a second amount of 10 cc. was withdrawn.

While the cannula was in the vein, the venous pressure was determined. Right-angled glass tubing was attached to the cannula, with the arm of the patient resting flat on a pillow at the level of the auricle, and the rise of the blood column in the tube was noted (method of Taylor, Thomas and Schleiter [16]). The tube was removed, 0.25 cc. of a freshly prepared 3 per cent solution of sodium cyanide was injected and, noting the time with a stop-watch, the first evidence of rapid or deep respiration with a sigh was recorded, which gave the pulmonary circulatory time (Robb and Weiss [17] method). We have also, recently, employed the glucoside method of Fishberg, Hitzig and King.[18]

The height, weight and age of each patient were noted, for a determination of body surface area. Vital capacity was determined by means of a Collins spirometer. The pulse rate and blood pressure were also noted.

To each of the four amounts of blood collected was added a 10 per cent solution of anticoagulant of the following mixture: ammonium oxalate, 2 Gm.; sodium chloride, 0.8 Gm., and distilled water to make 100 cc.

From each of the two specimens of blood not containing dye, 1 cc. was withdrawn to be utilized for a hematocrit determination (packed red blood cells). The remainder and the two samples of blood containing the dye were placed in separate centrifuge tubes and centrifugated for from thirty to forty-five minutes at a speed of 3,500 revolutions a minute to allow a separation of the blood into packed cells and plasma. The plasma levels were then separated into different test tubes.

Ten cubic centimeters of the plasma not containing dye was used to make up a fresh standard by adding to it and thoroughly mixing with it exactly 0.03 cc. of trypan red dye solution (weighed in a special weight glass on an analytic balance).

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15. A fresh solution of trypan red was made daily as follows: 0.6 per cent trypan red added to 50 cc. of physiologic solution of sodium chloride and 50 cc. of distilled water were heated in a small beaker and stirred until the mixture boiled. This was filtered twice and distilled water added to bring the total amount to 100 cc.

16. Taylor, A. A.; Thomas, A. B., and Schleiter, H. G.: A Direct Method for the Estimation of Venous Pressure, Proc. Soc. Exper. Biol. & Med. **27**:867 (May) 1930.

17. Robb, S. P., and Weiss, Soma: A Method for Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, Am. Heart J. **8**:650 (June) 1933.

18. Fishberg, A. M.; Hitzig, W. H., and King, F. H.: Measurement of the Circulation Time with Saccharin, Proc. Soc. Exper. Biol. & Med. **30**:651 (Feb.) 1933.

This mixture constituted the standard for each patient, and the plasma containing dye was compared with it under a Duboscq colorimeter. The standard plasma not containing dye was placed in the left colorimeter cup at 20 on the scale division, and plasma containing dye was placed in the right colorimeter cup, after which five readings were taken for each specimen by two different observers (protocol) and the average determined.

The two centrifuge tubes, each containing 1 cc. of blood not containing dye, were placed opposite each other in a special centrifuge and centrifugated at a rate of 10,000 revolutions a minute for thirty minutes. Then, the height of the packed cell column was read off directly in percentage from the hematocrit centrifuge tube, and the average of the two hematocrit values was utilized to determine the total circulating blood volume.

EXAMPLE OF PROTOCOL

Date. 1/20/32
Name. Mr. H. G.
Diagnosis. Duodenal ulcer
Weight. 57 Kg.
Height. 5 feet 9 inches (175.2 cm.)

Surface area. 1.67 square meters
Vital capacity. 2,500 cc.
Circulatory time (cyanide). 18 seconds
Venous pressure. 12 cm.

Amount of dye injected. 10 cc.
Standard. 10 cc. plasma plus 0.03 mg. dye
Hematocrit reading: 44; 44. Average, 44 ($44 \times 1.1 = 48.4$ corrected [K])

Standard of Duboscq colorimetric reading at 10 mm.

3 min. specimen	6 min. specimen
11.2	10.8
10.8	10.7
10.8	10.9
10.7	10.8
11.2	10.9
10.9	10.8

Average, 10.8

$$\frac{Cl}{Cx} = \frac{Sx}{Sl} \qquad \frac{100}{Cx} = \frac{10.8}{10} \qquad x = 92.6\ (e)$$

$$\text{Total plasma volume} = \left(\frac{100 \times f\ (P + a)}{a \times e} - f\right) \times \left(1 - \frac{0}{\frac{(100 - K) \times b}{100}} + 0\right)$$

$$\left(\frac{100 \times 10\ (10 + 0.03)}{0.03 \times 92.6} - 10\right) \times \left(1 - \frac{2}{\frac{(100 - 48.4) \times 20}{100}} + 2\right)$$

$$\left(\frac{1{,}000 \times 10.03}{2.778} = 3610.5 - 10.0\right) \times \left(1 - \frac{2}{\frac{(51.6 \times 20)}{100} + 2} = 1 - 0.162 = 0.838\right)$$

$3{,}600.5 \times 0.838 = 3.016.8$ total plasma volume

$$\text{Blood volume} = \frac{100}{(100 - K)} \times \text{plasma} = \frac{100}{(100 - 48.4)} \times \text{plasma} = \frac{100}{51.6} \times \text{plasma}$$

$1.93 \times 3{,}016.8 = 5{,}822.42$ total blood volume

$\frac{3{,}016.8}{57\ \text{Kg.}} = 52.9$ cc. plasma volume per kilogram

$\frac{3{,}016.8}{1.67\ \text{sq. meter}} = 1{,}805$ cc. plasma volume per square meter of surface area

$\frac{5{,}822.4}{57} = 102.1$ cc. blood volume per kilogram

$\frac{5{,}822.4}{1.67} = 3{,}486$ cc. blood volume per surface area

K indicates hematocrit value from blood volume cells (absolute volume of erythrocytes, with dilutions considered); P, volume of oxalated plasma used for a standard; a, weighed volume used for dilution of the dye; b, volume of sample of dye; O, 1 cc. + 1 cc. of oxalate solution; e, reading of unknown against standard (percentage of dye against standard), and f, volume of injected dye solution.

CRITIQUE OF METHOD

The question arises as to whether the dye method gives a sufficiently correct estimate of the total circulating blood volume to be of clinical value. We have found it to be the most reliable and adaptable of all infusion methods; it gives an exact determination of the circulating plasma volume, although not an absolutely exact determination of the circulating blood volume. However, by using hematocrit values, the circulating blood volume can be determined so accurately as to be of substantial clinical value. Absorption of the dye by the blood cells is entirely negligible, as shown by washing the cells. The following stipulations, however, must be kept in mind when utilizing the dye method to determine the total circulating blood volume: 1. The dye must be absolutely harmless. 2. There must be sufficient sojourn of the dye in the blood stream to permit its absorption by the plasma. 3. There must be equal diffusion of the dye through the blood. 4. The dye selected must be one that will not change in its chemical constituents in the blood stream; hence colloidal dyes are to be preferred.

RESULTS

In Normal Persons.—In the normal person we found that the plasma volume per kilogram of body weight varied from 36 to 49 cc., an average of 40.5 cc., and that the total circulating blood volume varied from 66 to 90 cc. per kilogram of body weight, or an average of 78.4 cc. The hematocrit values varied from 36.5 to 50.5 cc. with an average of 43.8 cc. The total circulating plasma volume averaged 2,780 cc., and the total circulating blood volume 5,386 cc. The pulmonary circulatory time by the Robb and Weiss method was between twelve and eighteen seconds, averaging sixteen seconds. Venous pressure values ranged from 3 to 5 cc., averaging 4 cc.

Comparing the values of our normal controls (table 1) with those of other authors (table 2) one notes the striking constancy of values obtained by the colloidal dye method. This is particularly noticeable in the values of the blood volume per kilogram of body weight. The carbon monoxide method, as utilized by Chang, is seen to give much lower values than those obtained by the colloidal dye method.

Variation of Blood Volume Under Physiologic Conditions.—For the circulation to function properly, blood must be distributed to all the tissues, particularly to the tissues that are at work. The regulatory mechanism for this is more peripheral than central. The blood must be utilized as economically as possible as it passes through the tissues, so that there is a sufficient reserve in time of necessity. This is manifested by the correlation between the total circulating blood volume

TABLE 1.—*Blood Volumes of Normal Adults in the Recumbent Position*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.
															Systolic	Diastolic			
1	Thu	M	64.0	61.3	63	1.65	2,446	38.2	1,482	4,951	77.3	3,000	80.7	46.0	110	65	84	14	3
2	Fle	M	68.0	68.0	71	1.87	3,369	49.0	1,802	5,625	82.0	3,008	82.0	36.5	110	70	80	12	5
3	Wei	M	71.0	71.8	71	1.89	2,866	40.3	1,514	6,442	90.7	3,403	90.0	50.5	100	70	82	18	4
4	Gin	M	72.7	72.7	69	1.74	2,915	40.0	1,675	5,532	76.0	3,041	76.0	43.0	100	50	82	17	4
5	She	M	57.2	63.6	66	1.62	2,425	42.3	1,499	4,851	84.9	3,000	76.2	45.0	110	70	80	16	5
6	Sha	M	63.1	58.1	63	1.65	2,709	42.9	1,639	5,036	79.6	3,052	86.6	42.0	110	80	76	17	4
7	Sus	M	85.4	60.4	64	1.90	3,162	37.2	1,664	6,000	70.2	3,150	99.0	43.0	100	80	80	18	5
8	Mur	M	70.0	65.9	67	1.80	2.533	36.6	1,407	4,709	67.2	2,616	71.1	42.0	100	70	80	17	4
9	Mor	M	63.6	66.3	66	1.68	2,747	43.1	1,635	5,004	78.6	2,978	75.4	41.0	80	65	76	17	4
10	Gra	M	72.7	66.3	68	1.83	2,633	36.0	1,438	5,713	78.0	3,121	86.1	49.0	110	70	76	21	4
Average.....			68.7	65.4	66	1.76	2,780	40.5	1,575	5,386	78.4	3,037	82.3	43.8	103	70	79	16	4

and the minute volume. If there is no correlation in the periphery, there may be poor utilization of the blood, so that there is an increase in the minute volume, hence an excessive demand on the central circulatory system, the heart and blood vessels. Because the minute volume shows how much blood is pumped out by the heart per minute, it may be considered a criterion of cardiac ability. The amount of minute volume is affected, among other factors, by functional variations in the amount of circulating blood volume and by the amount of blood emptied

TABLE 2.—*Reported Average Values for Circulating Blood Volumes, Utilizing Carbon Monoxide or Dye Method*

Author	Method	Total Plasma Volume	Per Kg. of Body Weight	Total Blood Volume	Per Kg. of Body Weight
1. Chang, H. C., and Harrop, G. A., Jr.: J. Clin. Investigation **5**: 393, 1928	Co	.....	..	4,263	66
2. Ewig and Hinsberg; Ztschr. f. klin. Med. **115**: 677, 1931	Co	.....	..	4,700	73
3. Waterfield, R. L.: J. Physiol. **72**: 110, 1931	Co	2,980	41	5,244	71
Average for carbon monoxide method	....	.....	..	4,735	70
4. Basok, M. Y., and Shesterikova, T. L.: Klin. Med. **22**: 1076, 1931	Dye	.....	40	.....	74
5. Ernst, C., and Stagelschmidt, P.: Ztschr. f. d. ges. exper. Med. **73**: 678, 1930	Dye	2,945	40	5,340	80
6. Greisbach, W., in Bethe, A., von Bergmann, G., Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928, vol. 6	Dye	2,309	36	4,514	71
7. Martinez, Carrasco: Ztschr. f. klin. Med. **117**: 540, 1931	Dye	3,415	57	6,112	100
8. Rowntree, L. G.; Brown, G. E., and Roth, G. M.: Volume of Blood in Health and Disease, Philadelphia, W. B. Saunders & Company, 1929	Dye	3,350	52	5,710	83
9. Ruznak, S.: Deutsches Arch. f. klin. Med. **157**: 186, 1927	Dye	.....	44	.....	82
10. Seyderhelm and Lampe: Ergebn. d. inn. Med. u. Kinderh. **27**: 245, 1925	Dye	.....	47	.....	83
11. Uhlenbruch, P., and Vogels, S.: Ztschr. f. klin. Med. **118**: 172, 1931	Dye	2,700	42	5,650	79
12. Wollheim, Ernst [5]	Dye	.....	40	5,336	80
Average for dye method	....	2,944	44	5,427	81
A. A. Goldbloom, I. Libin and P. K. Roht	Dye	2,780	40	5,386	78

into the heart during diastole (diastolic filling).[19] However, changes of blood volume do not follow corresponding changes of minute volume.

The yielding of blood in the capillaries to the tissues is dependent on the volume of blood in the capillaries, the pulmonary circulatory time and the composition of the blood. In a state of compensation, a minimum blood volume will circulate in normal circulatory time. The blood shows a compensatory state of polyglobulism, as evidenced by increased hematocrit readings, whereby more oxygen can be transported in a smaller amount of blood. At work, or after exercise, the fact of

19. The results of our studies of cardiac output will appear in a separate publication.

sufficient circulation is evidenced by an increase in the circulating blood volume in a correspondingly increased circulatory time. The minute volume also increases if there is sufficient reserve force in the heart. When there is no correlation between the minute volume expelled by the heart and the circulating blood volume, a hemodynamic disturbance of necessity manifests itself.

Studies have been carried out by a number of workers to determine the influence of various factors on the circulating blood volume. The factors fall mainly into three general groups: hematogenous, pharmacologic and humoral. Some of the factors causing a physiologic increase in the blood volume are: hematogenous, including low atmospheric pressure (lessened oxygen pressure) and inhalation of carbon dioxide; pharmacologic, including epinephrine, barium chloride, caffeine, camphor, strychnine sulphate, pituitary extract and thyroid extract, and humoral, e. g., exercise. Some of the factors causing a physiologic decrease in the blood volume are: hematogenous, including high atmospheric pressure (heightened oxygen pressure), diets poor in salt and nitrogen, and increased inhalation of oxygen; pharmacologic, including digitalis, histamine, morphine and peptone, and humoral, comprising postoperative shock, sitting or standing posture and sleep.

Alterations in Blood Volume Due to Pathologic Factors.—Hyperthyroidism: Nine cases of hyperthyroidism were studied, and the average total circulating blood volume was found to be one and a half times greater than that of normal persons. The increase in the circulating blood volume corresponded with an increase in the plasma volume. The hematocrit values were slightly increased, and the circulatory time (twelve seconds) was more rapid than normal. The venous pressure, however, was within normal range (table 3).

It is usually assumed that increased circulating blood volume is a compensatory mechanism because of increased consumption of oxygen, as evidenced by an increased basal metabolic rate. However, we noted that whereas under therapy with compound solution of iodine the basal metabolism is diminished there need not be a simultaneous effect on the circulating blood volume. The latter may diminish much later than the basal metabolic rate. It is possible that the increase in blood volume in our cases was governed by a special hormonal effect of the thyroid activity on the spleen, causing an outflow of blood hoarded in that depot. The forcing of such hoarded blood, with its corpuscular elements, into the blood stream would serve to explain the absence of anemia and the presence of lymphocytosis in thyrotoxicosis.

All of these patients were slightly underweight, and their blood pressure showed, on the average, only a moderately increased systolic value and a normal diastolic value, giving increased pulse pressure. The

TABLE 3.—*Blood Volumes of Patients with Hyperthyroidism Before Operation*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.	Basal Metabolic Rate
															Systolic	Diastolic				
11	Gor	F	55.0	62.2	64	1.57	2,771	50.3	1,765	7,481	136.0	4,764	120.2	58.5	130	80	96	10	7	+41
12	Hel	F	46.0	52.7	60	1.37	2,659	56.8	1,907	5,154	110.0	3,796	97.8	44.0	130	70	84	15	6	+44
13	Nac	F	61.3	55.9	60	1.55	3,431	56.0	2,213	6,347	104.0	4,094	113.1	42.0	115	70	88	18	4	+26
14	Gec	F	51.6	60.0	61	1.41	2,773	53.7	1,966	4,915	95.2	3,485	81.9	40.0	128	68	88	16	5	+40
15	Lev	F	38.5	55.9	59	1.28	2,635	69.0	2,058	4,690	124.0	3,664	83.8	40.0	140	80	88	13	6	+20
16	Wor	M	53.6	67.2	67	1.62	3,645	68.0	2,250	6,510	121.4	4,018	96.8	40.0	130	80	108	9	4	+50
17	Shl	M	55.0	68.1	65	1.63	3,275	59.5	2,009	6,486	117.9	3,979	95.2	45.0	120	60	120	10	6	+50
18	ShH	M	52.0	60.0	64	1.53	3,109	60.0	2,032	6,744	129.0	4,407	112.4	49.0	140	80	123	10	8	+60
19	Sta	M	66.0	73.1	69	1.66	3,238	49.0	1,947	6,018	91.1	3,622	82.3	42.0	138	70	110	11	8	+42
Average.....			53.2	61.6	64	1.51	3,059	58.0	2,023	6,038	114.2	3,981	98.1	44.5	130	73	100	12	6	+41

TABLE 4.—*Blood Volumes in Patients with Cardiovascular Disease with Decompensation Showing High Values (So-Called Plus Forms of Decompensation)*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg: Systolic	Blood Pressure, Mm. of Hg: Diastolic	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.	Comment
20	Gol	F	49.5	62.7	61	1.44	2,768	55.8	1,922	7,336	148.2	5,093	117.0	57.0	250	140	100	21	34	Decompensation, hypertension, orthopnea, edema
21	Fin	F	61.3	62.6	61	1.57	2,607	42.5	1,660	8,472	138.2	5,399	135.3	63.0	150	80	84	27	24	Decompensation, hypertension, orthopnea, edema
22	Hab	F	37.7	....	..	....	2,055	54.7	.....	4,440	118.0	.....	.....	49.0	118	70	76	..	18	Dyspnea, edema of feet, cyanosis, cor pulmonum
23	Sch	M	81.3	....	..	....	3,619	44.5	.....	7,527	92.5	.....	.....	47.5	120	100	108	..	14	Dyspnea, general edema, ascites, fibrillation, chronic coronary disease, loss of 27 pounds (12.2 Kg.) after operation
24	Sha	M	59.0	62.5	62	1.58	3,518	60.6	2,390	6,332	107.3	4,221	101.3	42.5	200	136	92	..	11	Dyspnea, cyanosis, decompensation, hypertension, coronary thrombosis, mesenteric lymph nodes
25	Mis	M	54.0	64.5	65	1.57	3,223	60.0	2,052	6,247	115.0	3,980	96.8	44.0	196	108	88	15	20	Decompensation, hypertension, edema, dyspnea
26	Hal	F	70.0	67.7	65	1.75	3,128	44.7	1,787	6,477	92.5	3,701	95.6	47.0	166	104	88	21	13	Decompensation, coronary disease
Average.....			58.9	64.0	62	1.58	2,988	51.8	1,961	6,690	115.9	4,479	109.2	50.0	171	105	90	21	19	

average basal metabolic rate was plus 41. The fact that in many of the patients there was no hypertension indicates that the presence of hypertension is not necessary to an increase in blood volume.

Cardiovascular Disease: Twenty-two cases of cardiovascular disease were studied (table 12), and the average blood volume determination was 95.9 cc. per kilogram of body weight. However, the twenty-two cases fall into two groups: seven showing an increased blood volume, averaging 115.9 cc. per kilogram of body weight (table 4) and fifteen showing a decreased blood volume, averaging 71.4 cc. per kilogram of body weight (table 5).

When there is no correlation between the minute volume expelled by the heart and the circulating blood volume, the clinical manifestations of the resultant disturbance are those of decompensation. Wollheim [20] classified two types of compensation, the "plus" and the "minus" forms, each group being determined by whether or not the blood volume is increased or decreased.

The average for our cases with the plus form of decompensation showed that this group had the greatest circulating volume in the series with the exception of the cases of polycythaemia vera (fig. 2). The high figures in the group with the plus form of decompensation were determined by an increase in both the plasma volume and the hematocrit determination (50 per cent of packed cells in the blood) in contradistinction to the figures for the cases of polycythaemia vera which showed a normal plasma volume and a very high hematocrit value (67.5 per cent of packed cells in the blood). The cases with the plus form showed a high venous pressure and high blood pressure, with a tendency toward symptomatic polycythemia. The cases studied were of the essential hypertensive type, showing left ventricular failure, chronic disease of the coronary artery and organic arteriosclerotic valvular (aortic or mitral) disease. The clinical survey of these patients generally revealed: wakefulness; restlessness; dyspnea, which was lessened if the patient sat with the legs hanging down over the edge of the bed; cyanosis of the prominent bony areas; greatly filled veins in the neck, the filling increased by pressure on the liver and increased blood volume. The cause of the cardiac disturbances in most of the cases was overwork and arrhythmia.

When one follows the improvement of the patient with the plus form of decompensation, with increased blood volume and venous pressure and prolonged pulmonary circulatory time under rest or therapy, it is noticed as a state of compensation is reached the blood volume and venous pressure diminish and the circulatory time returns to normal. Correspondingly, the patient with the minus form of decompensation in

20. Wollheim, E.: Klin. Wchnschr. **12**:12 (Jan. 7) 1933.

TABLE 5.—*Blood Volumes in Patients with Cardiac Disease with Decompensation Showing Low Values (So-Called Minus Forms of Decompensation)*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq. M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq. M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.	Comment
															Systolic	Diastolic				
27	Dia	M	71.0	66.0	64	1.75	3,196	44.5	1,826	6,455	89.0	3,698	97.8	46.0	170	70	42	14	18	Dyspnea, edema, heart block
28	Kle	M	63.6	66.0	67	1.71	2,855	44.9	1,669	4,365	61.4	2,552	66.1	32.0	130	70	70	..	6	Rheumatic fever, endocarditis, heart block, mitral stenosis
29	Gol	M	80.0	75.0	66	1.89	3,082	38.5	1,630	6,240	78.0	3,301	83.2	46.0	130	75	70	..	9	
30	Per	F	60.0	62.7	62	1.58	2,407	40.1	1,523	4,337	72.2	2,744	69.1	40.5	120	80	68	50	10	Chronic decompensated auricular fibrillation, orthopnea
31	Cha	F	74.5	62.7	62	1.75	2,832	38.0	1,618	4,605	61.8	2,631	73.4	35.0	112	60	70	21	19	Auricular fibrillation, cirrhosis of the liver, recurrent cardiac disease
32	Eps	M	82.0	70.4	67	1.89	2,697	33.0	1,370	4,496	54.8	2,715	63.8	36.0	200	130	70	..	5	Acute attack of coronary failure, intraventricular block, chronic cardiac disease, hypertension for 3 years
33	Har	M	65.0	70.4	67	1.70	2,591	39.8	1,524	5,132	79.0	3,018	72.8	45.0	120	80	72	..	3	Recurrent cardiac disease, intraventricular block, fresh coronary closure, large liver
34	Kra	M	66.3	65.9	64	1.69	2,451	36.9	1,450	4,714	71.1	2,786	71.5	45.0	146	112	120	..	12	Orthopnea and dyspnea (7 weeks), cyanosis, protodiastolic murmur, liver 2 fingerbreadths below costal margin, chronic cardiac disease
35	Gre	F	59.0	60.0	66	1.65	2,627	44.0	1,591	5,201	88.0	3,152	86.6	45.0	112	60	80	..	10	Rheumatic fever, endocarditis
36	Mis	M	63.0	61.3	62	1.61	2,673	42.4	1,641	4,143	65.7	2,513	67.5	36.0	170	100	90	13	4	Decompensation, hypertension, jaundice, diabetes
37	Bar	M	70.0	70.3	66	1.77	2,422	34.6	1,368	5,176	73.9	2,924	73.6	48.0	96	64	108	..	23	Orthopnea, pulmonary edema, chronic cardiac disease, acute coronary closure
38	Sei	M	50.0	58.1	64	1.50	2,216	44.3	1,477	4,486	89.7	2,990	77.2	46.0	130	70	100	15	19	Acute rheumatic fever with pericarditis
39	Bra	M	55.0	65.1	65	1.58	2,617	47.1	1,656	4,966	89.6	3,079	76.2	43.0	125	70	72	37	14	Button-hole mitral stenosis, orthopnea, edema, prominent venous pulsations, large liver, auricular fibrillation
40	Emi	M	72.0	61.2	63	1.74	1,822	25.0	1,047	3,255	44.0	1,807	53.1	40.0	130	80	88	15	11	Rheumatic fever
41	Fou	M	96.8	66.1	66	2.08	2,610	27.0	1,254	5,244	54.1	2,521	79.3	46.0	174	130	110	35	17	Orthopnea and dyspnea (3 years), general edema, scrotal edema, hypertension, heart gallop, loss of 36 pounds
Average.....			68.5	65.4	65	1.72	2,606	38.6	1,509	4,854	71.4	2,832	74.0	42.0	137	83	82	25	12	

a state of compensation shows an increase of the blood volume to a normal level, a normal circulatory time and a venous pressure that drops to normal in the majority of cases.

In the fifteen cardiac cases showing a decreased circulating blood volume, there was a tendency toward increased venous and blood pressure. The finding of a decreased blood volume per square meter of surface area was due to the diminished plasma volume and a normal hematocrit value. The majority of the patients were subject to recurrent rheumatic attacks, of either rheumatic endocarditis or rheumatic mitral disease, with or without auricular fibrillation. In a minority of the cases there was normal venous pressure (Mis, Har, Eps, Gol and Kle), and the patients presenting cyanosis and orthopnea gave the clinical impression of belonging to the group with the plus form of decompensation. However, they had, respectively, the following blood volumes per kilogram of body weight: 65.7, 79, 54.8, 78 and 61.4 cc. (table 5).

It is interesting to note that Bar, a patient with chronic disease of the coronary artery with left ventricular failure, should have shown a much higher circulating blood volume than 73.9 cc. per kilogram of body weight, taking into consideration also his decompensated state. However, there developed an acute coronary attack, during which he died, and it was this attack which produced the low circulating blood volume, although it did not fall to the level of the diminished blood volume in cases of shock or collapse. It is more than suggestive of these cases that coronary occlusion may be suspected when a diminished or low normal blood volume is encountered in patients in a state of decompensation with a previous history of left ventricular failure and hypertension, and presenting symptoms of orthopnea and dyspnea. The observations on venous pressure cannot be conclusive, because there is no increase or decrease in pressure simultaneous with the increase or decrease of the circulating blood volume.

In contradistinction to Bar, Sei, who had acute rheumatic fever with pericardial effusion, showed an increased blood volume and venous pressure, although one would have expected to find a low blood volume and a low venous pressure. This anomaly was explained, also, by observations at autopsy, which showed that adherent pericarditis had caused poor emptying of the left ventricle of the heart with increased pressure in the venous system and in the lesser circulation.

Clinically, the minus form of decompensation generally presents the following symptoms and signs: fatigue; drowsiness; dyspnea and orthopnea, lessened in a reclining position; cyanosis of the body and extremities; poor filling of the veins of the neck, not increased by pressure on the liver, and decreased circulating blood volume. The etiologic factor is generally arrhythmia, recurrent infections (such as endocarditis,

grip and angina) or chemical toxins, giving a sympathicotonic (vasomotor) effect.

The effect of infections on the circulating blood volume is due to increased protein decompensation which may be compared to the effect of peptone and histamine, which diminish the circulating blood volume. The dynamics of the minus form of decompensation begin with the opening of the capillary depots and the absorption of blood from the circulation. The circulating blood volume and the minute volume diminish simultaneously, owing to the lessened capacity of the veins and to the diminished diastolic filling of the heart due to the poor return of the venous blood. Clinically, patients with the minus form of decompensation show a similar effect of toxins on the capillaries; that is, there is a paralysis of the vasomotor centers causing vasomotor collapse.

It is important to differentiate clinically the cases of chronic cardiac disease showing a minus form of decompensation from cases of acute peripheral failure, as evidenced by shock and collapse. This is not true, however, except when there is acute coronary thrombosis and actually postoperative collapse. The differential points between the minus form of decompensation and vasomotor collapse are, briefly:

"Minus" Decompensation	Vasomotor Collapse or Shock
Chronic: many days to weeks	Acute, minutes to hours
Poor blood supply from dilated capillary depots, but arteriole tone present	Tone of splanchnic arterioles diminished
No drop in blood pressure	Marked drop in blood pressure
Blood volume moderately diminished	Blood volume markedly diminished
Venous pressure usually diminished, but may be increased	Venous pressure always markedly diminished, sometimes to an indeterminable point

Hypertension (Compensated): In the group of five patients with compensated hypertension we included those suffering from hyperthyroidism, essential hypertension, basophilic adenoma with hypertension and anemia. From our observations it appears that hypertension itself has no effect on the circulating blood volume, as it was either normal or at most only slightly diminished in all the cases in the group (table 6). When decompensation sets in, however, the blood volume is affected; the third greatest increase was noted in patients suffering from hyperthyroidism, but in most there was no hypertension. This condition disposes the patient to an increased blood volume, but since hypertension is not always present it is apparent that the increased blood volume is not a factor predisposing to hypertension.

Polycythaemia Vera: Seven patients presenting a severe form of polycythaemia vera were studied (table 7) and were found to have an increased total blood volume per kilogram of body weight and a high increase in hematocrit value. The average plasma value was somewhat

TABLE 6—*Blood Volumes in Compensated Hypertension Cases*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq. M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq. M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg: Systolic	Blood Pressure, Mm. of Hg: Diastolic	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.	Comment
42	Pep	F	57.0	62.7	62	1.56	2,727	47.9	1,748	5,401	94.7	3,462	86.1	45.0	190	110	80	..	7.5	Diabetes mellitus
43	Pea	F	45.4	64.5	65	1.46	3,075	67.5	2,196	5,000	110.1	3,424	77.5	35.0	186	56	100	15	10.0	Thyroid disorder, diabetes, hypertension, anemia
44	Wru	F	61.0	62.7	62	1.60	1,941	31.8	1,213	3,929	64.4	2,455	62.6	46.0	208	130	88	..	6.0	Basophilic adenoma
45	Ble	M	70.0	60.4	61	1.71	2,603	37.2	1,522	4,840	69.2	2,830	80.1	42.0	165	100	86	10	8.0	Hypertension
46	Kor	M	71.8	61.3	62	1.71	2,585	36.0	1,505	5,010	69.7	2,929	81.7	44.0	205	120	96	16	7.0	Hypertension
Average.....			61.0	62.3	62	1.60	2,586	44.0	1,618	4,836	81.6	3,020	77.6	42.4	190	103	90	13	7.7	

TABLE 7.—*Blood Volumes in Cases of Polycythaemia Vera*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq. M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq. M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg: Systolic	Blood Pressure, Mm. of Hg: Diastolic	Pulse Rate	Venous Pressure, Cm.	Circulatory Time (Cyanide), Seconds	Hemoglobin, per Cent (Sahli)	Red Blood Cells per Million
47	Tho	F	54.0	67.3	65	1.57	2,620	48.5	1,669	12,576	232.0	8,010	186.8	72.0	130	70	72	3	18	129.0	8,690
48	Bro	M	60.2	67.3	64	1.62	3,130	50.0	1,907	10,482	174.0	6,443	155.7	64.5	145	80	80	5	24	100.0	5,800
49	Dav	F	54.3	67.3	65	1.57	2,734	50.3	1,741	6,734	124.0	4,289	100.5	54.0	120	65	72	7	19	102.0	5,800
50	Mer	M	52.0	65.9	65	1.55	1,962	35.8	1,264	8,531	164.0	5,503	129.4	70.0	140	80	80	4	17	125.0	8,000
51	Hac	M	63.6	70.4	67	1.70	2,130	32.4	1,252	8,452	132.9	4,970	120.0	68.0	140	90	80	4	12	125.0	9,100
52	New	M	53.6	63.6	63	1.53	1,930	36.0	1,261	11,772	219.6	7,629	185.0	76.0	160	110	92	3	17	123.0	10,000
53	Mes	F	67.2	60.0	60	1.48	2,820	41.9	1,905	8,572	127.5	5,791	142.8	61.0	145	95	70	5	20	107.0	7,500
Average.....			57.9	65.9	64	1.57	2,475	42.2	1,571	9,589	167.7	6,090	145.7	67.5	140	84	78	4	18	115.8	7,840

TABLE 8.—*Blood volumes in Cases of Anemia (Varied)*

TABLE 8.—*Blood volumes in Cases of Anemia (Varied)*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg: Systolic	Blood Pressure, Mm. of Hg: Diastolic	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.	Hemoglobin, per Cent (Sahli)	Red Blood Cells per Million	Comment
54	Gol	F	67.2	59.3	60	1.62	3,825	56.9	2,361	5,163	76.8	3,187	87.3	24.0	115	70	96	13	18.1	30.0	3.300	Anemia, myxedema
55	Ste	M	67.9	55.4	62	1.65	3,241	49.0	1,958	4,991	73.5	3,024	90.0	32.0	125	75	80	14	4.5	31.0	3.400	Gaucher's disease spleen much enlarged
56	Kle	F	60.0	59.0	61	1.57	2,999	49.9	1,910	3,789	63.1	2,413	64.2	19.0	130	70	84	11	4.5	48.0	2.000	Pernicious anemia
57	Bru	M	53.6	59.0	64	1.54	2,9.8	55.6	1,999	4,508	86.0	2,985	77.8	32.0	125	70	90	14	8.0	40.0	3.000	Myeloblastic leukemia
58	Ros	M	63.6	64.0	66	1.68	2,444	38.4	1,454	4,280	67.2	2,548	66.9	39.0	120	80	78	..	5.0	54.0	3.750	Splenomegalic anemia
59	Rei	F	66.3	55.1	58	1.58	3,255	49.1	2,060	5,489	82.7	3,474	99.8	37.0	130	85	75	..	8.0	52.0	3.700	Spleen (immense), Wassermann 4 plus
Average.....			63.1	58.6	61	1.60	3,123	49.8	1,957	4,720	74.9	2,938	81.0	30.0	124	74	84	13	8.0	42.5	3.191	

TABLE 9.—*Blood Volumes in Cases of Metabolic Disorders*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg: Systolic	Blood Pressure, Mm. of Hg: Diastolic	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.	Comment
60	Hal	F	127.0	57.2	60	2.11	4,172	32.8	1,977	7,175	56.4	3,400	125.4	38.0	115	80	66	16	5	Obesity
61	Wra	M	50.0	61.8	66	1.52	2,119	42.4	1,394	3,785	75.7	2,490	61.2	40.0	95	70	70	16	4	Diabetes insipidus
62	Ros	M	100.0	67.2	67	2.10	2,946	29.4	1,403	5,965	59.6	2,840	88.7	46.0	130	70	76	24	8	Obesity, substernal thyroid disturbance
63	Lan	M	92.7	65.5	65	1.97	3,293	35.3	1,671	6,553	59.9	2,819	84.7	37.0	210	75	80	13	20	Obesity, hypertension
64	Cole	M	63.0	70.0	..	1.68	2,273	36.0	1,353	5,684	90.2	3,383	81.2	54.0	110	80	70	21	8	Cirrhosis of the liver
65	Myx	M	85.0	....	64	1.89	2,661	31.3	1,408	4,847	57.0	2,764	....	41.0	120	80	73	24	9	Myxedema
66	Nov	M	65.0	61.3	63	1.67	3,210	49.3	1,922	5,623	86.5	3,366	91.7	39.0	120	80	80	15	7	Nephrosis
Average.....			83.2	63.8	64	1.84	2,952	36.6	1,589	5,661	69.3	2,980	88.8	42.1	128	68	73	18	8	

less than normal and considerably less than in many other conditions. The venous pressure and circulatory time were normal except in the case of Bar, who showed decompensation.

In symptomatic polycythemia we found that the total blood volume is diminished and that the plasma volume is diminished or normal, while the number of erythrocytes and the hematocrit value are high, producing a state of polycythaemia normovolemia. In polycythaemia vera, on the other hand, the cell volume and blood volume are markedly increased, producing a volume status of polycythaemia hypervolemia. Although there was marked increase in the viscosity of the blood and a tendency to sluggish circulation, the circulatory time was actually only slightly affected. The main differentiating point was the high hematocrit value in polycythaemia vera.

Anemia: Six cases of anemia were studied, which included the following conditions: myxedema, Gaucher's disease, pernicious anemia, myeloblastic leukemia and splenomegalic anemia (table 8). When the total blood volume was normal, the blood volume per kilogram of body weight remained in the lower levels of normal. One wonders whether the mechanism that causes the increased plasma volume is not a compensatory or adaptive one, that is, a replacement factor.

Metabolic Disturbances: In the group of seven patients showing clinical manifestations of obesity, pituitary disease and basophilic adenoma, we found (table 9) that the hematocrit values were within normal range, but that the total circulating blood volume was markedly below normal, although it would probably rise to normal in the case of obese patients if the weight of the patient were ideal. In the obese patients the increased plasma volume closely followed the increase in body surface, but lagged far behind the increase in body weight. The fact that the blood volume lagged behind the plasma volume, compared with the increased body weight and surface area, suggests that cell volume by hematocrit readings is less in obese than in normal patients.

Avitaminosis (Scurvy): We had an opportunity to study one case of scurvy, and to our surprise found a tremendous increase in plasma volume, to one and a half times normal (table 10), far more than in the cases of anemia and metabolic disturbances. The blood volume per kilogram of body weight was particularly increased, but the hematocrit values were below normal. The high plasma volume would indicate that the primary damage is not in the capillaries but in the plasma itself, with a secondary disturbance in the capillaries, corresponding to the condition that Eppinger [21] described as a primary plasma disturbance in certain cases of trauma.

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21. Eppinger, H.: Die Blutreservoire des Menschen: Innere Medizin, Klin. Wchnschr. **12**:5 (Jan. 7) 1933.

TABLE 10.—*Blood Volume in a Case of Avitaminosis (Scurvy)*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.
															Systolic	Diastolic			
67	Rob	M	60.0	61.3	68	1.70	3,707	61.8	2,180	5,721	95.3	3,763	93.4	32.0	120	70	82	..	6

TABLE 11.—*Blood Volumes in Cases of Neurocirculatory Asthenia*

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.
															Systolic	Diastolic			
68	Pfe	M	76.3	63.6	67	1.89	2,105	26.0	1,113	4,079	53.0	2,159	64.1	44.0	110	80	84	12	4
69	Gol	M	55.0	62.3	65	1.58	2,813	51.0	1,780	5,228	95.0	3,309	83.7	42.0	95	60	80	18	5
70	Gol	F	53.6	60.4	64	1.55	2,606	48.6	1,681	5,396	100.0	3,481	89.3	47.0	120	75	80	18	5
71	Gol	M	68.1	70.9	70	1.83	2,889	42.4	1,578	6,583	96.6	3,597	92.8	51.0	115	80	80	18	4
72	Wol	F	65.0	56.9	61	1.61	3,066	47.1	1,904	5,700	87.7	3,543	100.1	42.0	110	70	80	12	5
73	Smi	M	69.8	62.2	62	1.69	2,527	36.2	1,495	5,177	74.1	3,063	89.6	46.0	140	90	88	16	4
Average.....			64.9	62.7	64	1.69	2,667	41.8	1,591	5,360	84.4	3,192	86.6	45.3	115	75	82	15	4

TABLE 12.—*Average Values for the Various Groups, Showing Circulating Blood Volume, Venous Pressure, Blood Pressure and Circulation Times*

Condition	Number Studied	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq. M.	Total Plasma Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Total Blood Volume, Cc.	Cc. for Each Kg. of Body Weight	Cc. for Each Sq.M. of Body Surface	Cc. for Each Kg. of Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm. of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm.
														Systolic	Diastolic			
Normal	10	68.7	65.4	66	1.76	2,780	40.5	1,575	5,386	78.4	3,037	82.3	43.8	103	70	79	16	4
Hyperthyroidism	9	53.2	61.6	64	1.51	3,059	58.0	2,023	6,038	114.2	3,981	98.1	44.5	130	73	100	12	6
Cardiac disease (combined)	22	61.6	66.2	63	1.65	2,647	48.1	1,782	5,772	95.9	3,655	84.8	46.5	159	94	86	23	14
Plus form	7	58.9	64.0	62	1.58	2,988	51.8	1,961	6,690	115.9	4,479	109.2	50.0	171	105	90	21	19
Minus form	15	68.5	65.4	65	1.72	2,606	38.6	1,500	4,854	71.4	2,832	74.0	42.0	137	83	82	25	12
Hypertension (compensated)	5	61.0	62.3	62	1.60	2,786	44.0	1,618	4,836	81.6	3,020	77.6	42.4	190	103	90	13	7.7
Polycythaemia vera	7	57.9	65.9	64	1.57	2,475	42.2	1,571	9,589	167.7	6,090	145.7	67.5	140	84	78	18	4
Anemia (varied)	6	63.1	58.6	61	1.60	3,123	49.8	1,957	4,720	74.9	2,938	81.0	30.0	124	74	84	13	8
Metabolic disorders	7	83.2	63.8	64	1.84	2,952	36.6	1,589	5,661	69.3	2,980	88.8	42.1	128	68	73	18	8
Avitaminosis (scurvy)	1	60.0	61.3	68	1.70	3,707	61.8	2,180	5,721	95.3	3,763	93.4	32.0	120	70	82	..	6
Neurocirculatory asthenia	6	64.9	62.7	64	1.69	2,667	41.8	1,591	5,360	84.4	3,192	86.6	45.3	115	75	82	15	4

Neurocirculatory Asthenia: The six cases in this group were typical in their clinical manifestations. In some of the patients the condition simulated thyrotoxicosis (flushed skin, tachycardia, rapid pulse and increased basal metabolic rate), but both the plasma volume and the total circulating blood volume were within normal limits instead of attaining the high limits found in the patients with hyperthyroidism (table 11). The venous pressure and circulating time were normal. These observations definitely aided our clinical impression that these

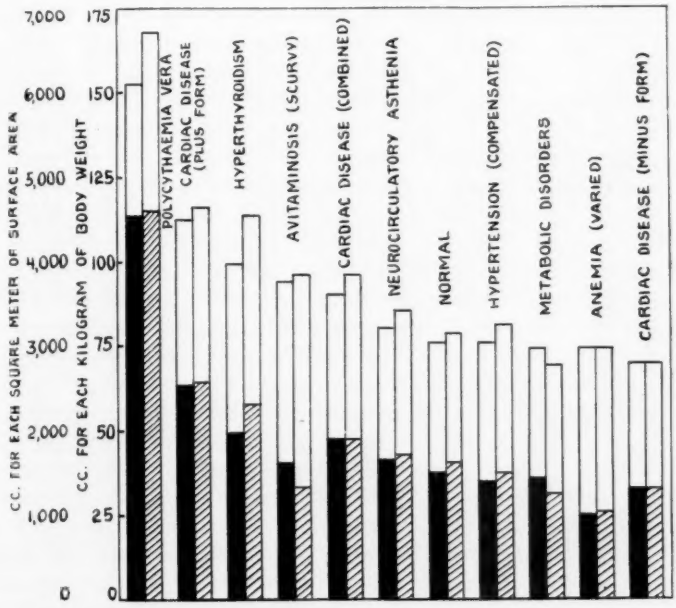

Fig. 2.—Circulating plasma volume and cell volume per square meter of body surface and kilogram of body weight in varied conditions. The solid columns indicate the plasma and cell volume for each square meter of surface area, and the cross-hatched columns the plasma and cell volume for each kilogram of body weight.

patients did not have thyrotoxicosis, but had borderline cases and a hyperthyroid constitution. The occurrence of a diminished blood volume at certain times in these cases would explain their orthostatic tachycardia and fatigue, headaches and dizziness. There was simultaneously a diminished cardiac output, with resultant poor nourishment of the tissues and skin.

COMMENT

As the average of our determinations of blood volume in normal persons was fairly identical with the average findings in normal persons reported by other authors carrying out an identical technic under exactly the same conditions, we consider that there is definitely a standard normal value, ranging between 67 and 90 cc. per kilogram of body weight, or an average of 78.4, and that the average normal circulating blood volume per square meter of body surface is 3,037 cc. There is less variation of body surface than of weight, hence the average circulating blood volume on the basis of body surface is a more exact average than the average per kilogram of body weight (fig. 2). However, the surface area of the patient is not estimated as a routine procedure, whereas weight is, so that circulating blood volume per kilogram of body weight is more often ascertained than blood volume per square meter of surface area.

Although our results showed a variation in the respective groups of patients studied, nevertheless the average for each group, as in normal persons, was fairly constant, particularly when averages of blood volume per square meter of surface area were estimated. It is understood that psychic and nervous influences can affect end-results, but this is not serious, as seen in the fact that although patients with hyperthyroidism and those with neurocirculatory asthenia are extremely nervous, the end-results in these cases were constant for each group. Clinically, the patient with neurocirculatory asthenia is a highly nervous person, yet his blood volume was less than normal, in contradistinction to the less nervous patient with hyperthyroidism who showed an increased blood volume. This is well demonstrated in a case reported not long ago,[22] in which cardiodynamic determinations served as a differential factor between neurocirculatory asthenia and hyperthyroidism. In the present series, the average blood volume per kilogram of body weight in hyperthyroidism was 114.2 cc. and in neurocirculatory asthenia, 84.4 cc.

Normally, there is a correlation between blood volume and minute volume, with a normal circulatory time. When there is no correlation, disturbance manifests itself in either a plus or minus form of decompensation, the plus form meaning increased and the minus form decreased circulating blood volume.

The clinical symptoms and signs in cases with a plus form of decompensation consist of orthopnea, dyspnea, restlessness, cyanosis of the bony projections, marked distention of the jugular veins,

22. Goldbloom, A. A.: Diagnostic Importance of Blood Volume and Cardiac Output Studies in a Borderline Case of Thyrotoxicosis, M. Clin. North America **17**:279 (July) 1933.

enlarged liver and edema. In our group we found such conditions as decompensated essential hypertension, decompensated coronary disease with or without auricular fibrillation, decompensated arteriosclerotic valvular (aortic or mitral) disease and cor pulmonum. The etiologic factor was usually overstrain or arrhythmia.

In the cases with the minus form of decompensation the predominant symptoms and signs were fatigue, sleepiness, absence of dyspnea in the prone position, poorly filled jugular veins (filling not increased by pressure on the liver) and generally cyanosis. In this group we found such conditions as acute rheumatic fever, recurrent rheumatic endocarditis, auricular fibrillation (rheumatic), acute coronary occlusion, compensated hypertension with or without heart block and jaundice. The etiologic factors were recurrent infection, with their effects.

The differentiation of cardiovascular conditions into the plus or minus form of decompensation as based on the physiologic facts is of interest from the therapeutic standpoint. Certain drugs (caffeine, camphor, epinephrine and extract of the posterior lobe of the pituitary gland) tend to increase the blood volume, while others (histamine, digitalis, morphine and peptone) cause a decrease. The plus form of decompensation is caused by the failure of the peripheral circulation to carry adequate oxygen to the tissues, causing anoxemia, which stimulates the bone marrow and produces an excess of red blood cells. This is one explanation of why in the majority of cases showing the plus form of decompensation we found symptomatic polycythemia. The minus form of decompensation is caused, in the majority of cases, by an infectious factor which has an effect on the system similar to that of peptone, which diminishes the blood volume. An additional causative factor would seem to be an increase in the amount of blood hoarded in the various blood depots, because autopsy in these cases often reveals enlargement and congestion of the blood-hoarding organs. We found that in acute coronary occlusion with collapse caffeine and epinephrine are valuable, whereas in chronic coronary conditions these drugs are contraindicated.

We feel that the number of cases is too small for us to be dogmatic in our opinion and that further clinical studies are indicated. We have used the physiologic facts as a guide to therapy. In the minus forms of decompensation we have used drugs tending to increase the blood volume, as mentioned previously, while in the plus forms such drugs as digitalis and morphine have been of service. We do not wish to imply that in the minus form of decompensation digitalis is always contraindicated or that in the plus form digitalis is always indicated. It will require much more experience and evaluation of all the other factors before a definite stand can be taken on the question.

It is important to differentiate between the case showing the minus form of decompensation and one of shock or collapse. Although it is believed by some that the minus form of decompensation is actually a manifestation of collapse, our studies have shown that this is not true and that there are several points which differentiate the two conditions.

The outstanding observation in cases of polycythaemia vera was that the blood volume was increased to more than two and a half times normal; in fact, these showed the highest circulating volume of all the cases in our series, the second highest being the group with the plus form of decompensation. This high determination of blood volume is due to the increased hematocrit value in association with a normal or subnormal plasma volume. The high hematocrit value is a means of differentiating polycythaemia vera from polycythaemia symptomatica.

The case of scurvy was unusually interesting in that it gave the highest plasma volume in the series, and yet the total circulating blood volume was normal, owing to the low hematocrit value. Our impression is that the excessive plasma volume represents a primary disturbance in the plasma and that the capillary disturbance is secondary.

The conditions that showed an increase in blood volume in this series were the following: hyperthyroidism, hypertension with auricular fibrillation, complete heart block, disease of the coronary artery, arteriosclerotic valvular disease (mitral or aortic), chronic emphysema and bronchitis with decompensation and polycythaemia vera.

The conditions that showed a decreased blood volume were: acute rheumatic fever, recurrent rheumatic endocarditis, rheumatic valvular lesions (mitral), compensated hypertension, anemia (leukemia, secondary anemia and pernicious anemia), metabolic disturbances (obesity, basophilic adenoma and myxedema), neurocirculatory asthenia and avitaminosis (scurvy).

SUMMARY

Experimental work has shown that there are various blood depots, such as the spleen, liver, subpapillary plexus of the skin, large veins and lungs. Hence, there are two forms of blood volume: active circulating blood volume and passive hoarded blood volume. Clinically, the term blood volume refers to active circulating blood volume. A detailed description of the method and technic employed to determine the blood volume in seventy-three cases and the results are presented.

CONCLUSIONS

Although present clinical methods of determination of the blood volume may not be fool-proof, nevertheless our results, with the colloidal dye method described, have substantiated the belief that determination of the blood volume is not only of clinical value, but should be more widely utilized than at present.

Our observations show that hypertension, in itself, does not increase blood volume. Therefore, in cases of thyrotoxicosis with hypertension, it is not the hypertension that is the cause of the increased blood volume. We have ascertained, also, that there is no relationship between increased basal metabolic rate and increased blood volume.

Cases of chronic cardiovascular disease fall, by determination of the blood volume, into two groups, the plus and minus forms of decompensation, the former indicating increased and the latter decreased blood volume. This division is important, not only therapeutically, but because when there is a change from a plus to a minus form of decompensation the existence of an acute coronary condition may be suspected. A minus form of decompensation is not identical with decreased blood volume due to shock or collapse, as there are clinical factors to differentiate them.

The determination of the blood volume is particularly helpful in the differential diagnosis of hyperthyroidism and neurocirculatory asthenia, and of polycythaemia vera and symptomatic polycythemia.

Progress in Internal Medicine

BRIGHT'S DISEASE: A REVIEW OF RECENT LITERATURE

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While this review of the subject of nephritis is intended primarily to summarize the most recent developments in that field, it is impossible to do so without going back into the literature of the past twenty years to trace the outlines of the growth of the present concepts and to give orientation to the discussion. I wish to state frankly at the outset that I have made no attempt to give a complete bibliography, even of the literature of the past year. Keeping in mind the desirability of clarity and the necessary limitation of space, I have sought to digest the great mass of literature and to quote key articles from which a more detailed bibliography can be obtained.

The modern trend of thought about Bright's disease began to crystallize twenty years ago with the publication of "Die Brightsche Nierenkrankheit," by Volhard and Fahr,[1] who introduced an anatomic and pathogenic classification of Bright's disease consisting of three main types, glomerulonephritis, nephrosis and nephrosclerosis. Following this Addis[2] adopted a clinical classification correlated with quantitative studies of the formed elements in the urinary sediment and with the renal lesions. The nomenclature of Addis may be readily translated into that of Volhard and Fahr. The hemorrhagic type of Bright's disease, or glomerulonephritis, is characterized by hematuria, acute, chronic or intermittent. The diffuse forms tend to be associated with hypertension (not regularly) and with nitrogen retention and inflammatory glomerular lesions. The degenerative forms of Bright's disease, or the nephroses, are characterized in the main by edema and proteinuria without hypertension or hematuria and by degenerative changes confined within the

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1. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

2. Addis, Thomas: A Clinical Classification of Bright's Disease, J. A. M. A. **85**:163 (July 18) 1925.

kidney to epithelial structures. The arteriosclerotic forms of Bright's disease, or the nephroscleroses, are characterized clinically by a marked hypertension preceding serious renal signs and histologically by arteriolar sclerosis.

A third great step forward came with the work of Van Slyke and his collaborators,[3] who published a monograph in 1930 in which the nosography of Bright's disease was enriched by the addition to the clinical picture of chemical and physiologic studies incident to observations on the courses of the different types of the disease. Van Slyke and his co-workers employed the classification of Addis, his method of enumerating the formed elements in the urinary sediment, all the modern resources for the chemical examination of the blood with particular reference to the proteins of the blood and urine, and the urea clearance test which was developed in Van Slyke's laboratory for the measurement of renal function. The resultant changes in renal anatomy which they were able to observe became doubly significant in view of the careful clinical and functional studies preceding them. This monograph stands as a masterpiece, one of the best examples of modern clinical investigation in which clinical, physiologic and morphologic methods are perfectly welded.

Minor readjustments have become necessary in the modern classification of Bright's disease as outlined in the preceding paragraphs. Some of these readjustments will be discussed subsequently. The most complete treatment of the entire subject available in English is found in the work of Fishberg.[4] A review by Fahr[5] covers the recent German literature only.

In most of the progressive American clinics the urinary sediment count (Addis) has become a procedure almost as firmly fixed as the blood cell counts. Hines[6] has recently devised a nomograph which greatly simplifies the computations and at the same time gives indications as to the magnitude of the errors involved.

Most of the achievements of modern medicine have depended on knowledge of the causes of disease and on ability to deal with them so as to achieve prevention or cure. The importance of a simple accurate classification of renal disease lies in the fact that such a classification is an

3. Van Slyke, D. D.; Stillman, E.; Møller, E.; Erich, W.; McIntosh, J. F.; Leiter, L.; McKay, E. M.; Hannon, R. R.; Moore, N. S., and Johnston, C.: Observations on the Courses of the Different Types of Bright's Disease and on the Resultant Changes in Renal Anatomy, Medicine **9**:257, 1930.

4. Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

5. Fahr, T.: Beiträge zur Frage des Morbus Brightii, Klin. Wchnschr. **13**:45, 1934.

6. Hines, D. C.: A Nomograph for Simplifying Computation of the Urine Sediment Count (Addis), Am. J. M. Sc. **187**:841, 1934.

essential step in the process of relating specific causes to specific effects. In studying the pathologic conditions in the kidneys the importance of careful cytologic differentiations is becoming increasingly appreciated, particularly in regard to a comparison of lesions produced experimentally in animals with those observed post mortem in human beings. Two papers by McGregor [7] deal with the application of these methods to the study of the finer histology of the normal glomerulus and of the cytologic changes occurring in clinical glomerulonephritis. In the second article she traced the processes of endothelial proliferation, hyaline fiber formation and extracapillary changes through various stages up to the point of glomerular obliteration. Absence of exact morphologic criteria lies at the bottom of most of the differences of opinion which exist among various investigators who have endeavored to produce diffuse glomerulonephritis experimentally. The difficulty is well illustrated in a recent report by Rieder and Balzer.[8] After a critical review of all the experimental attempts to produce diffuse glomerulonephritis, including their own experiments, these authors concluded that so far no one has produced with certainty anything more than focal nephritis. They admitted the close resemblance to glomerulonephritis of the lesions produced by the American investigators Duval and Hibberd, who injected a Berkefeld-filtered lysate of the peritoneal exudate of rabbits which had been inoculated intraperitoneally with scarlatinal streptococci after having been previously immunized against them.

GLOMERULONEPHRITIS AND RHEUMATIC FEVER

The opinion is widespread among students of Bright's disease that there is some relationship between hemorrhagic nephritis and streptococcic infection. In rheumatic fever a somewhat similar relationship is suspected, though in neither disease has the exact nature of the relationship been made clear. For this reason recent investigations into the incidence of glomerulonephritis in rheumatic fever arouse considerable interest and are of theoretical importance. Using the urinary sediment count, Goldring and Wykoff [9] found that the excretion of formed elements and of protein occurred in excess of normal in a series of sixteen cases of acute rheumatic fever. The abnormal excretion rate continued for from four

7. McGregor, L.: The Finer Histology of the Normal Glomerulus, Am. J. Path. **5**:545, 1929; Cytological Changes Occurring in the Glomerulus in Clinical Glomerulonephritis, ibid. **5**:559, 1929.

8. Rieder, W., and Balzer, E.: Ueber Versuche zur Erzeugung einer akuten diffusen Glomerulonephritis, Ztschr. f. d. ges. exper. Med. **92**:517, 1934.

9. Goldring, W., and Wykoff, J.: Studies of the Kidney in Acute Infection: I. Observations with the Urine Sediment Count (Addis) in Acute Rheumatic Infection, J. Clin. Investigation **8**:569, 1930.

to ten weeks after the subsidence of the acute attack. A direct relationship was noted between the height of the fever and the quantitative abnormalities of the urine. No mention was made of the possible relationship of the urinary abnormalities to the antirheumatic remedies employed.

In a discussion of the glomerular lesions associated with endocarditis Bell [10] found evidence of diffuse glomerulitis in 22 per cent of a considerable series of cases of rheumatic endocarditis. The lesions are described as follows:

> Nearly all the glomeruli are involved. There is a definite increase in the number of endothelial cells and their cytoplasm has become conspicuous. The capillary basement membrane is occasionally thickened. . . . Occasionally there is also a notable increase in the number of leucocytes in the glomerular capillaries.

The changes were less pronounced than in the usual clinical cases, though in two instances the endothelial proliferation was quite prominent. Embolic lesions of the glomeruli were also noted in a small number of cases.

Baehr,[11] on the other hand, commented on the extreme rarity of glomerulonephritis in true rheumatic endocarditis, regarding it as an accidental complication and not a characteristic of the disease. He [12] expressed the belief that the intercurrent appearance of nephritis or a nephritic syndome in a case which has been regarded as one of rheumatic endocarditis justifies doubt as to the accuracy of the diagnosis. Such a condition is much more likely to be subacute bacterial endocarditis in the bacteria-free stage, in which the incidence of glomerulonephritis is 33 per cent, the so-called atypical verrucous endocarditis of Libman or a renal manifestation of peri-arteritis nodosa.

It is not yet clear why two such careful workers as Bell and Baehr arrived at such different conclusions. It may be that there are geographic differences in the severity and type of rheumatic lesions, local differences in management of the cases or differences in the criteria used in the histologic diagnosis of the renal lesions. One must also assume that clinical opinions may differ somewhat about the differential diagnosis of simple rheumatic endocarditis, the bacteria-free stage of subacute bacterial endocarditis and the other atypical endocarditides mentioned by Baehr.

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10. Bell, E. T.: Glomerular Lesions Associated with Endocarditis, Am. J. Path. **8**:639, 1932.

11. Baehr, G.: Renal Complications of Endocarditis, Tr. A. Am. Physicians **46**:87, 1931.

12. Baehr, G., and Schifrin, A.: The Rarity of Glomerulo-Nephritis in Rheumatic Fever and Its Significance, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 1, p. 125.

In a very recent report Blaisdell [13] described the renal lesions found at autopsy in sixteen cases of rheumatic fever. A nonsuppurative periarteritis affecting the smaller arteries and arterioles was found in eight cases, perivascular scarring in four cases and a recurrent type of inflammation in two cases. Blaisdell did not observe the typical rheumatic arteritis of Pappenheimer and von Glahn in any of his cases. The arterial lesions bore a close resemblance to the perivascular lesions seen in the myocardium in rheumatic fever. Glomerular lesions were found in one case only, in close association with the arterial lesions and believed to be dependent on them.

NEPHRITIS AND THE TOXEMIAS OF PREGNANCY

The time has come when it is possible to study the renal diseases in pregnancy by the same methods as those used for renal disease in nonpregnant persons. Much of the confusion which has surrounded the subject in the past will disappear when modern methods of detecting renal disease are used at the onset of pregnancy and when the renal sequelae of the toxemias of pregnancy are followed up by such methods. Ambiguous and useless terms such as "low reserve kidney" will be discarded. Latent glomerulonephritis antedating pregnancy will be more frequently detected. In such cases some of the acute renal phenomena occurring later in pregnancy will be better understood, and they may be more frequently avoided.

Addis has classified the renal lesions of the toxemias of pregnancy under the heading of the degenerative type of Bright's disease, in spite of the concomitant hypertension and vascular lesions. The importance of the latter factors cannot be overlooked, however, and there is increasing evidence that the renal lesions of pregnancy should be grouped with the nephroscleroses rather than with the nephroses.

Bell [14] described the renal lesions of eclampsia and pre-eclampsia. He found a characteristic glomerular lesion in which the lumens of the capillaries are narrowed by a thickening of the basement membrane and sometimes by a slight or moderate endothelial proliferation. He stated that the thickening of the capillary basement membrane is characteristic of the kidneys in all forms of hypertension. In all of his patients in whom eclamptic phenomena were noted in nephritis preceding pregnancy autopsies revealed the presence of the characteristic lesions of diffuse glomerular nephritis. In one case lesions resulting from eclampsia which occurred seven years previously were described. They consisted of focal

13. Blaisdell, J. L.: The Renal Lesions of Rheumatic Fever, Am. J. Path. **10**:287, 1934.

14. Bell, E. T.: Renal Lesions in the Toxemias of Pregnancy, Am. J. Path. **8**:1, 1932.

hyaline areas in the glomeruli with partial or complete glomerular obliteration and varying degrees of tubular atrophy, together with the fresh lesions of the second attack of eclampsia which caused death. Regarding the pathogenesis, Bell was inclined to reject the Volhard theory of angiospastic ischemia in spite of the fact that glomerular ischemia was a regular finding and that symmetrical cortical necrosis sometimes occurs. Bell favored the theory of a circulating toxin. The glomerular lesions of eclampsia were described originally by Loehlein. They are also described by Baird and Dunn [15] who confirmed the observations of Bell.

Gibberd [16] called attention to the significance of recurrence of the late toxemias of pregancy. Observations were made on an unselected group of previously normal women in whom late toxemias of pregnancy developed, the criterion of which was the occurrence of renal albuminuria not associated with pyelitis or infection. It was found that a first toxemia may affect a previously healthy woman in one of three ways: It may immediately give rise to a chronic nephritis; it may be followed by more or less habitual recurrence in subsequent pregnancies, the kidneys being apparently normal and the patient healthy in the intervening periods, or it may leave the patient entirely normal. To explain the second group Gibberd proposed the theory of an "occult nephritis." It accords well with the clinical facts, but it lacks anatomic support, unless one considers the case of Bell in which healed lesions resulting from a previous eclampsia were noted. Gibberd advocated the early induction of labor in the first toxemia in order to diminish the definite risk of a chronic nephritis (which occurs in from 10 to 15 per cent of patients) and the greater risk of an occult nephritis (reported in from 40 to 50 per cent).

DEGENERATIVE FORMS OF BRIGHT'S DISEASE—THE NEPHROSES

It has been assumed by most recent workers that a true genuine or "lipoid" nephrosis exists, in spite of the fact that the nephrotic stage of glomerulonephritis presents an almost identical syndrome of common occurrence. The true lipoid nephrosis, if it exists at all, appears to be exceedingly rare. Patients presenting this syndrome have been studied at autopsy by competent observers with the occasional finding of a case in which inflammatory glomerular lesions were absent. Fahr and others have described degenerative lesions of the glomeruli in a few of these patients and have even described a type of contracted kidney which they consider to be secondary to degenerative lesions of the glomeruli.

15. Baird, D., and Dunn, J. S.: Renal Lesions in Eclampsia and Nephritis of Pregnancy, J. Path. & Bact. **37**:291, 1933.

16. Gibberd, G. F.: The Significance of Recurrence of the Late Toxemias of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **41**:23, 1934.

Bell [17] studied, post mortem, the kidneys of ten patients who were assumed to have had lipoid nephrosis. All ten were considered by Bell to have a form of glomerulonephritis in which the glomeruli were damaged without sufficient obstruction of the capillaries to interfere with glomerular function or to cause tubular atrophy.

While such observations on ten patients do not exclude the possibility that a true lipoid nephrosis exists, they indicate the need of extreme caution in making that diagnosis unless the entire clinical course of the disease has been subjected to intensive scrutiny with particular reference to the presence of blood in the urine.

Concerning renal amyloidosis, Dixon [18] collected one hundred cases from 9,813 consecutive autopsies. Tuberculosis had been the etiologic factor in 78 per cent of the cases, malignant tumors in 9 per cent, intrathoracic suppuration in 7 per cent and chronic osteomyelitis in 1 per cent. Amyloid deposits in the glomeruli accounted for the renal insufficiency, but deposits in the smaller arteries were also regarded as playing a rôle. It was found that amyloid deposits occasionally occurred in other types of chronic nephritis.

NEPHROSES DUE TO HEAVY METALS

Bernard and Rossier [19] have described in considreable detail the renal and urinary abnormalities which may develop in a small percentage of cases of tuberculosis in the course of treatment with salts of gold. The most common phenomenon is a transient albuminuria. Sometimes the symptoms of azotemia and oliguria are noted. In severe forms lumbar pain, anuria, massive albuminuria, edema, hematuria and uremic symptoms are observed. Death may occur, but recovery generally ensues if the patient does not succumb in the acute stages. In general, the severity of the phenomena observed is proportional to the size of the dose administered. Cases are on record in which there were cumulative insults to the kidneys resulting from an injudicious repetition of doses before the effects of previous doses had disappeared. In other cases there was much evidence to suggest hypersusceptibility to injury by gold preparations analogous to the marked intolerance sometimes exhibited toward arsenic, in that severe renal damage followed the administration of relatively small doses. Bernard and Rossier discussed the factors which may enter into the production of the renal lesions. While it is probable that gold preparations alone account for the majority of cases, some other toxic factor must be postulated in order to account for those in

17. Bell, E. T.: Lipoid Nephrosis, Am. J. Path. **5**:587, 1929.

18. Dixon, H. M.: Renal Amyloidosis in Relation to Renal Insufficiency, Am. J. M. Sc. **187**:401, 1934.

19. Bernard, E., and Rossier, A.: Sur la néphrite par les sels d'or, Paris méd. **1**:28, 1934.

which acute nephritis occurs. This additional factor may have something to do with the reaction in tuberculosis which follows the use of gold salts. Mention is made of the observations of other workers which suggest that gold salts occasionally hasten or cause the rapid development of amyloidosis.

Vallery-Radot, Gilbrin and Gauthier-Villars [20] described the renal lesions produced experimentally in animals by injection of large doses of gold salts. Black casts were found in the convoluted tubules after repeated injections, varying in number according to the amount of gold preparation given. No renal lesions were observed except those in the convoluted tubules. Glomerular lesions and desquamative changes in the collecting tubules were never found.

One of the most important contributions in the past year is the announcement by Rosenthal [21] of an effective antidote for acute mercury poisoning. This antidote is sodium formaldehyde sulphoxylate, a powerful reducing agent by means of which the toxic mercury compounds are reduced to the mercurous state or to metallic mercury. The procedure recommended by Rosenthal is quoted in detail as follows:

> Gastric lavage is done through a stomach tube with a 5 per cent solution of sulphoxylate, approximately 200 cc. of this solution being left in the stomach. Immediately following this, 10 Gm. dissolved in from 100 to 200 cc. of distilled water is slowly injected intravenously, from twenty to thirty minutes being permitted for the injection. From four to six hours after the completion of this injection the intravenous administration of from 5 to 10 Gm. of sulphoxylate may be repeated in severe cases. If it is feasible to test the blood serum against corrosive mercuric chloride, the time that this reaction becomes faintly positive or negative (from three to five hours) may be taken as an indication of the time to give this second intravenous dose of sulphoxylate. If colitis later develops, I employ high colonic irrigations with a 1:1,000 solution of sulphoxylate once or twice daily.

Such treatment is said to be highly effective even when given as late as an hour and a half after the ingestion of the mercury.

ARTERIOSCLEROTIC FORMS OF BRIGHT'S DISEASE—THE NEPHROSCLEROSES

Of cases in which pronounced hypertension precedes serious renal signs many clinicians recognize a benign and a malignant type. In the benign type nephrosclerosis rarely advances to renal insufficiency. The malignant form of nephrosclerosis progresses rapidly to the uremic

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20. Vallery-Radot, P.; Gilbrin, E., and Gauthier-Villars, P.: Mode d'élimination du métal dans les néphrites expérimentales par les sels d'or, Presse méd. **41**:1827, 1933.

21. Rosenthal, S. M.: Mercury Poisoning, J. A. M. A. **102**:1273 (April 21) 1934.

stage. Hematuria is not characteristic of the benign type, but it commonly occurs in the malignant form of nephrosclerosis, a fact which creates some confusion in interpretation and a difficulty in differential diagnosis between glomerulonephritis and malignant nephrosclerosis.

An interesting and important study of a patient with malignant hypertension and nephrosclerosis has been made by Weiss, Parker and Robb.[22] Their patient had hematuria arising from the left kidney, of such severity that this kidney was removed. At the operation, performed under spinal anesthesia, functional tests were carried out, and the oxygen content of blood from the renal artery and renal vein was determined. Control observations of a similar character were made on three subjects in whom the kidneys were normal and on whom operations for the suspension of a mobile kidney were performed under spinal anesthesia.

The difference in the oxygen content between the arterial and the venous blood in normal kidneys was about 2.4 per cent, and the amount of oxygen utilized by the kidneys was 13 per cent of the average oxygen content of the arterial blood. In the patient with malignant hypertension the oxygen content of the venous blood was actually higher than that of the arterial blood, owing to the increased concentration due to loss of water. The results indicated that there was an excessively rapid flow of blood through the glomerular and tubular capillaries under the force of an elevated arterial pressure. The authors inferred that there is a high intratubular pressure as well as a rapid flow of the filtrate through the tubules, which accounts for the dilatation of these structures observed histologically. Microscopic examination showed glomeruli with a characteristic thickening of capillary basement membranes and in various stages of hyalinization. During the interval of sixty-seven days which elapsed between the nephrectomy and the examination of the right kidney at autopsy there occurred a great increase in the proportion of glomeruli with thickened basement membranes and of those with complete sclerosis. The hematuria was believed to have resulted from the rupture of glomerular and tubular capillaries under the stress of a greatly increased capillary pressure.

Another study of the histologic changes observed in the kidneys in malignant hypertension is that of Cain,[23] who reviewed the literature on the subject. In his study the major emphasis is laid on the arteriolar changes.

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22. Weiss, S.; Parker, F., Jr., and Robb, G. P.: A Correlation of Hemodynamics, Function and Histological Structure of the Kidney of Malignant Arterial Hypertension with Malignant Nephrosclerosis, Ann. Int. Med. **6**:1599, 1933.

23. Cain, E. F.: Malignant Hypertension: The Histologic Changes in the Kidneys, Arch. Int. Med. **53**:832 (June) 1934.

In considering the etiology of the nephroscleroses one must consider that of the hypertension on which they depend. A review of the literature is beyond the limited scope of this article. One etiologic factor is worthy of more than cursory discussion, however.

Certain agencies have recently called attention to the widespread dissemination of lead in foods as a result of the spraying of fruits and vegetables and of other processes of metallic contamination. This knowledge has resulted in a great renewal of interest in the toxic properties of lead. From Queensland has come a report by Fairly [24] of a governmental inquiry as to the importance of lead as a causative factor in chronic nephritis, which condition was found to be three times as common in people under 40 years of age in Queensland as in other Australian states. Typical lead poisoning occurs more commonly in the children of Queensland. Investigation showed that a large proportion of the children with lead poisoning died of chronic nephritis before the age of 40. The report describes the manner in which the children acquire lead from weathered lead paint on verandas to which they are often confined. Regulations are recommended which would prohibit the use of lead in paints on toys, furniture, pencils and verandas. It is also urged that stringent limitations be put on the use of lead arsenate for the spraying of fruits and vegetables. In the analyses it was found: "Of 31 samples of cabbage, 29 showed from 3 to 20 grains [from 0.195 to 1.30 Gm.] of lead arsenate per cabbage."

TESTS OF RENAL FUNCTION

Two methods of testing the functional capacity of the kidneys have been gaining steadily in vogue. These are the urea clearance test of Møller, McIntosh and Van Slyke [25] and the creatinine clearance test of Holten and Rehberg.[26] The significance and relative accuracy of these tests have been studied by several workers. Hayman and Johnson [27] carried out experiments to determine the relation of the results of these two tests to the number of glomeruli found in the human kidney at

24. Fairley, K. D.: A Review of the Evidence Relating to Lead as an Aetiological Agent in Chronic Nephritis in Queensland, M. J. Australia **1**:600, 1934.

25. Møller, E.; McIntosh, J. F., and Van Slyke, D. D.: Relationship Between Urine Volume and Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427, 1928; Relationship Between Urine Volume and Rate of Urea Excretion by Patients with Bright's Disease, ibid. **6**:485, 1928.

26. Holten, C., and Rehberg, P. B.: Studies on the Pathological Function of the Kidneys in Renal Disease, Especially Bright's Disease, Acta med. Scandinav. **74**:479 and 538, 1931.

27. Hayman, J. M., Jr., and Johnson, J. M.: Experiments on the Relation of Creatinine and Urea Clearance Tests of Kidney Function and the Number of Glomeruli in the Human Kidney Obtained at Autopsy, J. Clin. Investigation **12**: 877, 1933.

autopsy. They employed Kunkel's modification of Vimtrup's method in which glomeruli were counted in a suspension of digested kidney after injection at constant pressure of potassium ferrocyanide and ferric ammonium citrate and digestion with hydrochloric acid. Counts of injected and uninjected glomeruli were also made in blocks of kidney after embedding and sectioning. In the kidneys of twelve persons without any evidence of renal disease the counts for one kidney ranged from 800,000 to 1,530,000; the mean was 1,156,000 and the standard deviation 191,266. The results of creatinine and urea clearance tests were compared with the number of glomeruli found in a series of patients on whom the tests were performed shortly before death. In both glomerulonephritis and the arteriosclerotic form of Bright's disease the reduction in the clearance as shown by the tests was associated with a reduction in the number of injected glomeruli. In pneumonia and pyelonephritis the clearance may be reduced in the presence of a normal number of glomeruli. It is suggested that this is due to the back diffusion of the test substances through damaged tubular cells. These facts suggest that the clearance tests may be taken as the measure of the amount of functioning renal tissue only in the absence of toxic factors producing damage to the tubular cells.

Hayman, Halsted and Seyler [28] made a comparison of the creatinine and the urea clearance both in normal persons and in those with Bright's disease. The variability of the two tests from the mean normal was approximately the same but was of considerable magnitude. For the maximum urea clearance the range was from 38 to 112 cc. per minute, with an average of about 75 cc. The mean standard urea clearance was 51 cc., with a range from 30 to 67 cc. and a standard deviation of 10.11 cc. In regard to the creatinine clearance test Hayman, Halsted and Seyler pointed out that results must be as low as 60 cc. per minute to be considered definitely abnormal, although the mean creatinine clearance in one hundred and thirty observations on fifty-nine normal subjects was 148 cc. per minute. A creatinine clearance of from 60 to 80 cc. per minute is doubtfully normal but indicates an abnormal condition if a repetition of the test gives results in the same range.

The creatinine clearance test is based on studies made by Rehberg which led him to believe that creatinine is not resorbed by the tubules and that it can be used, therefore, to study the rate of glomerular filtration. Hayman and his co-workers expressed the belief that their observations cast doubt on the nonresorbability of creatinine and indicate that it does not measure glomerular filtration under all conditions. While this would invalidate the conclusions of some experiments based on

28. Hayman, J. M., Jr.; Halsted, J. A., and Seyler, L. E.: A Comparison of the Creatinine and Urea Clearance Test of Kidney Function, J. Clin. Investigation **12**:861, 1933.

Rehberg's assumptions, it would not necessarily destroy the value of the creatinine clearance test as a clinical test of renal function.

Lassen and Husfeldt [29] took advantage of the opportunity of studying the creatinine clearance in young men with a normal heart and normal kidneys before, during and after the marked change in blood pressure occurring under spinal anesthesia. At the height of the anesthesia, when the fall in blood pressure was most marked, they found a great decrease in glomerular filtration as calculated from the creatinine, the decrease being proportional to the fall in blood pressure. At the same time the concentration index $\frac{\text{Concentration of Creatinine in Urine}}{\text{Concentration of Creatinine in Blood}}$ increased significantly, indicating that the tubular function was normal as far as the resorption of water was concerned. The great decrease in the volume of urine which occurred during the fall in pressure was due partly to the great resorption of water and partly to the low volume of glomerular filtrate. They found that diuresis could be kept near normal if racemic ephedrine and caffeine were used to maintain the blood pressure at a higher level.

In contrast to the observations just cited, Page [30] found that fluctuations in blood pressure exercised little influence on the urea clearance. The fluctuations which he induced in hypertensive patients by sodium sulphocyanate or by colloidal sulphur did not impair the efficiency of urea clearance. The fluctuations observed were not comparable in extent to those observed by Lassen and Husfeldt,[29] and they affected the systolic blood pressure to a much greater extent than the diastolic.

Alving and Van Slyke [31] have investigated the significance of the widely used concentration and dilution tests. They found that concentration tests are sensitive for qualitative detection of damaged renal function but not suitable for measuring its extent. For instance, following acute nephritis the concentration test may show abnormal results for a long time after the urea clearance has returned to normal. In chronic nephritis the concentration may not decrease while the urea clearance falls to the uremic level. In general, it may be said that the urea clearance measures the function of excreting nitrogen and that the concentration test measures the function of excreting mineral salts. Alving and Van Slyke did not discover any useful information contributed by the dilution tests.

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29. Lassen, H. C. A., and Husfeldt, E.: Kidney Function and Blood Pressure, J. Clin. Investigation **13**:263, 1934.

30. Page, I. L.: The Effect on Renal Efficiency of Lowering the Blood Pressure in Cases of Essential Hypertension and Nephritis, J. Clin. Investigation **13**:909, 1934.

31. Alving, A. S., and Van Slyke, D. D.: The Significance of Concentration and Dilution Tests in Bright's Disease, J. Clin. Investigation **13**:969, 1934.

PATHOLOGIC PHYSIOLOGY OF BRIGHT'S DISEASE

The biochemical aspects of the great functional derangements of Bright's disease manifested in uremia, acidosis and edema have been dealt with in an encyclopedic way by Peters and Van Slyke.[32] Since that time no observations of fundamental significance have been added to the knowledge of uremia and its almost invariable concomitant acidosis.

In dealing with the subject of uremia it will materially assist the student to familiarize himself with the differentiation between "true" and "false" uremia which Volhard [33] has proposed. The "false" uremic phenomena in the sense of Volhard are those which may be embodied under the concept of "hypertensive encephalopathy," namely, eclamptic seizures, transient focal neurologic disturbances, Cheyne-Stokes breathing, etc., all of which may be observed in hypertensive states in the absence of renal insufficiency. The "true" uremia includes only the phenomena which result from the failure of renal function, namely, anorexia, nausea, vomiting, hyperpnea of the Kussmaul type, stupor, coma, the associated increases in the nonprotein nitrogenous constituents of the blood and the alterations in blood electrolytes. Peters and Van Slyke [32] made it clear that the nitrogen retention is not the cause of these phenomena, though it is a good measure of their intensity. In general, the theories of uremia which are based on the retention of a hypothetic toxin are inadequate to explain all the facts. A far more satisfactory working concept of uremia results if one considers it as a breakdown of the normal regulatory functions of the kidneys in their contribution to the maintenance of the internal environment of the cells constantly in an optimal state. In such a concept retention phenomena play a part, as evidenced by the retention of nonprotein nitrogen, inorganic acid radicals and aromatic oxacid. Of equal importance are the failures of the kidney to retain and conserve essential substances, for instance, the failure to retain fixed bases which results from the breakdown of the ammonia-forming function of the kidneys. In the abnormal states of equilibrium between inorganic and organic acids and bases and in the state of hydration of the body, failures both of retention and of excretion and compensatory readjustments of extrarenal mechanisms play a part.

EDEMA IN NEPHRITIS

The biochemical and biophysical phenomena of edema have also been exhaustively reviewed by Peters and Van Slyke [32] up to 1931. To

32. Peters, J. P., and Van Slyke, D D.: Quantitative Clinical Chemistry Interpretations, Baltimore, Williams & Wilkins Company, 1931.

33. Volhard, F.: Nieren und ableitende Harnwege, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1931, vol. 6, pts. 1 and 2.

this field of study Peters has been one of the principal contributors. Many years ago Starling called attention to the importance of the osmotic pressure of the serum proteins in relation to the intracapillary pressure in maintaining the balance of water exchange through a capillary wall. From this as a starting point great advances have been made in the understanding of the pathologic physiology of edema.

Weech [34] has very recently given a clear, terse review of the known facts regarding the relationships of oncotic pressure, capillary pressure, capillary permeability, protein content of the lymph, lymph flow, elasticity of the tissues, mechanical pressure in tissue spaces, variations in salt intake and certain renal factors in diuresis. These are the best known of the variable factors which must be considered in an analysis of the mechanism of edema. Weech referred particularly to the more recent work of Drinker and Fields, of Landis and of Schade and Clausen, who have been important contributors to this field.

I have occasionally observed patients without edema in whom the values of the serum proteins and colloidal oncotic pressure were below those at which Moore and Van Slyke [35] commonly found edema to occur. Of particular interest in this connection are some comparisons made by Weech of values for lymph protein and serum protein in normal and in edematous dogs, which indicate that in some of the cases of edema with low serum proteins the capillary walls become less permeable than normal, since the ratio of serum protein to lymph protein was 4.4 in normal as compared with 16.1 in edematous animals. He also measured the relationship of the oncotic pressure of the serum to the rate of lymph flow. In a group of normal dogs an average oncotic pressure of 20.7 mm. of mercury was accompanied by an average lymph flow of 1.71 cc. in ten minutes; in edematous dogs with an average pressure of 9.1 mm. of mercury the lymph flow was 2.09 cc. in ten minutes. These findings suggest a partial answer to the question why abnormally low serum proteins are not always accompanied by edema. Kylin [36] suggested another factor which must not be overlooked. He observed a case of nephrosis in which the colloid oncotic pressure of the blood fell as low as from 100 to 150 mm. of water without any detectable edema. He called attention to the fact that Leiter [37] produced edema experimentally by the com-

34. Weech, A. A.: Fluid Distribution and Edema, Bull. New York Acad. Med. **10**:269, 1934.

35. Moore, N. S., and Van Slyke, D. D.: The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930.

36. Kylin, E.: Zur Frage der Pathogenese des Nephroseoedems, Acta med. Scandinav. **80**:403, 1933.

37. Leiter, L.: Experimental Nephrotic Edema, Arch. Int. Med. **48**:1 (July) 1931.

bined process of decreasing the plasma proteins (plasmapheresis) and giving the animals large quantities of salt. Kylin decreased the colloidal oncotic pressure of the blood of fifteen dogs to the level of from 50 to 100 mm. of mercury. Salt was not given, and edema did not occur, from which facts Kylin concluded that the hydropigenous action of salt is essential to the production of edema by diminished colloidal oncotic pressure.

The special interests of the reviewer have centered on the factors concerned in the regeneration of the plasma proteins when these have become depleted by inanition or by excessive albuminuria. A brief outline of these factors has recently been presented.[38]

The first workers who made an experimental attack on the problem of regeneration of serum proteins were Kerr, Hurwitz and Whipple,[39] who discovered that in normal conditions there were reserves of serum proteins, since these bodies were replaced during fasting after one or two depletions by plasmapheresis. They also found that regeneration was more rapid when the experimental animals were fed liver rather than beef or milk as a source of protein. That the liver plays an important rôle in this regeneration is shown by the delay in replacement of plasma proteins after injury of the liver or after the production of an Eck fistula.

It has long been known through the advocacy of Epstein that large amounts of protein in the diet exert a beneficial effect in the management of lipoid nephroses. Keutmann and McCann[40] in undertaking a study of regeneration of plasma protein in glomerulonephritis found it necessary to determine whether or not the use of diets high in protein had any adverse effects on the course of the disease. They were able to show only beneficial effects, since hematuria, quantitatively measured, was not increased and functional tests showed improvement. These studies have been continued for more than two years, but so far only a preliminary statement of the results has been given.[38] It has been found that protein may be readily stored in the body in glomerulonephritis when given in adequate amounts and subjected to the sparing action of a liberal supply of carbohydrate and fat. The difficulty encountered was that of increasing the amount of proteins in circulation in the plasma.

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38. McCann, W. S.: The Clinical Significance of the Plasma Proteins, New York State J. Med. **34**:923, 1934.

39. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Proteins: I. Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion, Am. J. Physiol. **47**:356, 1918; Regeneration of Blood Serum Proteins: II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion, ibid. **37**:370, 1918.

40. Keutmann, E. H., and McCann, W. S.: Dietary Protein in Hemorrhagic Bright's Disease, J. Clin. Investigation **9**:973, 1932.

In some cases the plasma proteins did not increase appreciably in spite of an enormous deposition of protein.

Lepore [41] has shown that a close relation exists between the concentration of plasma protein and plasma volume. Whipple and his co-workers [42] have shown that the total amount of plasma protein decreases during starvation but that this decrease is masked by a simultaneous shrinkage in plasma volume, so that the percentage of protein is not much altered even when the total amount circulating is reduced to one-half the normal. It is known that the amount of plasma proteins cannot be increased above normal by means of high protein diets. Holman, Mahoney and Whipple [43] found that when the reserves of plasma proteins are depleted by plasmapheresis the regeneration of new plasma proteins can be controlled at will by dietary measures. Liver and casein and some vegetable proteins were found to be efficient in promoting regeneration. These authors found that before testing the efficiency of various foods the protein reserves of the test animals should first be exhausted. Globulin was found to be more easily regenerated than albumin, small amounts of it being produced even on their basal diet which contained only a little protein (from potato). A reversal of the albumin to globulin ratio occurred in some patients on the basal diet alone and in all patients with plasmapheresis on the basal diet. With a liver diet the production of albumin exceeded that of globulin.

The same investigators found that large amounts of blood plasma can be given intravenously to normal dogs over a period of several weeks without any significant loss of protein in the urine. Dogs could be kept in nitrogen equilibrium when they received sugar orally and plasma intravenously. When plasma was fed by mouth under identical conditions the urinary nitrogen was a little higher, a fact which suggests that injected protein is utilized more completely. Holman, Mahoney and Whipple concluded that "all these facts point to a *dynamic equilibrium* between tissue protein and plasma protein depending upon the physiological needs of the moment." Elsewhere [38] attention has been called to the analogy which may be drawn between the relation of glycogen to blood sugar and the plasma protein reservoir to amino-acids. Depletion of the plasma protein reservoir may be the result of inanition, of loss of protein in the urine or of any factors leading to a negative nitrogen balance. The reserve may be restored by adequate nutrition. Overfilling is probably prevented by the specific dynamic action of protein.

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41. Lepore, M. J.: Relation of Plasma Volume to Plasma Protein Concentration, Proc. Soc. Exper. Biol. & Med. **30**:268, 1932.

42. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet, J. Exper. Med. **59**:251, 1934.

43. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Given by Vein Utilized in Body Metabolism, J. Exper. Med. **59**:269, 1934, footnote 42.

These facts have been extensively reviewed because of their obvious importance in the dietary management of Bright's disease, in particular of the nephrotic syndromes. As pointed out elsewhere,[44] protein which is being deposited makes no demand on the excretory function, so that it is possible in many cases to build up the nutritive condition of patients whose renal function has been reduced to the uremic stage, with the result that life and capacity to work have not infrequently been prolonged.

Until the specific causes of the various types of Bright's disease can be dealt with in prevention or cure, treatment must be largely dependent on skilful management of the nutritional requirements, particularly with regard to proteins, bases and hematopoietic substances, together with such adjustment of the water and chloride intake as the need for diuresis and tendency to edema may require.

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44. McCann, W. S.: The Many Sided Question of Protein in Nephritis, Ann. Int. Med. **5**:579, 1931.

Book Reviews

Periodic Fertility and Sterility in Woman. By Prof. Dr. H. Knaus. With a foreword by Prof. F. H. A. Marshall, F.R.S., Cambridge. Authorized English translation by D. H. Kitchin and Kathleen Kitchin, M.Sc., M.B., B.S., London. Price, $6; post-free, $6.50. Pp. 160, with 64 illustrations and 12 tables. Vienna: Wilhelm Maudrich, 1934.

An ideal method of controlling conception, it has been said, must be harmless and convenient and must not offend taste or esthetic sensibilities; it should not affect sensation, it should be easily applied and it should be cheap and safe. The Ogino-Knaus method, it is claimed, fulfils all these requirements, with the possible exception of a certain amount of inconvenience. Periods of abstinence are required, but this is probably not a serious difficulty. Furthermore, the method has the approval of the church and the synagogue. Whether it is really safe is still a matter of discussion. The authors claim it to be so in 90 per cent of cases, as large a percentage of effectiveness as has been demonstrated for any of the mechanical and chemical devices available. The failures are attributed to very irregular menstruation, poor general health, disobedience and inadequate attention on the part of the women to keeping accurate records of their menstrual cycles.

On the other hand, critics of the method point out that conceptions are known to have taken place during the Ogino-Knaus "safe period," and that this alone throws doubt on the underlying theory; that more women menstruate irregularly than regularly, contrary to the contention of Knaus, and that the frequency with which a woman's rhythm may be upset by such trivial incidents as unusual physical exercise or change of climate, as is admitted by Knaus, makes the method unreliable. Hartman, whose work with monkeys supports the theory maintained by Knaus, stated: "That the prevailing opinion that ovulation may occur at any time of the cycle cannot be brushed aside without much further proof, at least so far as the human species is concerned."

Whatever the outcome of this discussion, the "safe period" of Ogino and Knaus has aroused such general interest and has been so widely discussed in newspapers, periodicals and several popular books that the physician will welcome this exposition of the subject by Knaus, the present monograph representing the summation of all his previous papers on the subject.

The translation is exceptionally satisfactory. The biologic basis of conception is considered briefly but adequately, and the author's method of determining the date of ovulation in woman is discussed in detail. It depends on graphic records of the effect of injections of solution of pituitary on uterine tone, the reaction to pituitary being lost on the day when ovulation is predicted and secretion of the hormone of the corpus luteum begins. It is concluded that ovulation occurs on the fifteenth day before the onset of the next period, when the reproductive physiology is normal. The corpus luteum has an autonomous function regularly lasting fourteen days, not only in the human being but also in many other species.

The need for precise recording of the dates of menstruation in determining the character of the cycle in the individual is discussed, and a menstrual calendar is described. "In the case of irregular cycles the ovulation date may be on any day in the period of time which falls between the two ovulation dates of the shortest and longest cycles respectively, the cycles being recorded for at least twelve months."

The final chapters are devoted to Ogino's contributions, a historical review of the idea of periodic fertility and the scientific evidence by which this method of the prevention of conception is supported.

Amoebiasis and Amoebic Dysentery. By Charles F. Craig. Price, $5. Pp. 315, with 54 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

The recent rapid advances in the knowledge of amebiasis have left the average physician not only behind but in a state of confusion. The old concept of amebic dysentery as a drastic disease confined more or less to the tropics has been shattered, and it is claimed that 10, 20 or even 50 per cent of healthy persons pass cysts of pathogenic amebas in the feces, and, what is even worse, actually have some disability as a result of the infestation. One was shocked to hear recently of a large outbreak of acute dysentery in one of our greatest cities, and there are reports on every hand of new drugs which are said to be better than the old standby emetine, and with most of which the general practitioner has had little chance to experiment.

The time is clearly ripe for an authoritative summary of the whole problem, and no pen is better qualified to write this than that of Colonel Craig, long a student in the field of amebiasis. Three hundred and five pages of text with many pictures of parasites and specimens of tissue, together with tables and charts, describe the history, epidemiology, pathology, clinical manifestations and treatment. The newer anti-amebic drugs are discussed critically with reference to both acute dysentery and the carrier state, and each chapter is followed by a list of useful references.

With only one phase of Colonel Craig's exposition would the reviewer take issue—the question of the carrier and the alleged symptoms of the carrier state. In table II on page 45 is set forth the incidence of positive results of examinations of the stools as made by various workers in different parts of the country. The figure varies from 0.2 per cent in the series of Andrews and Paulson in Baltimore to 53 per cent among the students of the University of California as reported by Kofoid. Among a total of 49,336 persons studied in various surveys, 11.6 per cent harbored Amoeba histolytica, and this Craig believes to be a fair average figure. When one turns, however, to the symptoms which are said to result from the carrier state the situation is much less convincing. Indeed, the reviewer fears that Craig, firm in his belief, fails to see the weakness of his case when he states that carriers of amebas suffer from gas, constipation or diarrhea, disturbances of appetite, loss of weight, headache, sleepiness and disturbed slumber, poor memory, nervous instability, slight elevations of temperature or subnormal temperature, poor circulation (whatever that may mean), sallow skin and tenderness over the abdomen. Obviously this catalog would fit equally well a dozen other disorders, even such entirely unrelated ones as hypertension or chronic brucellosis. As the significance of the carrier of Ameba histolytica is the most important part of the whole problem of amebiasis from the standpoint of both individual and public health, one regrets that this subject has been dealt with somewhat from the standpoint of the special pleader.

Studies on Blood Sugar and Glycosuria in Exophthalmic Goitre. By William Thune Andersen. Pp. 206, with 16 illustrations. Copenhagen: Levin & Munksgaard, 1933.

This book contains the author's thesis for the doctorate of medicine at the University of Copenhagen. The material comprised thirty-one patients with exophthalmic goiter and two with diabetes mellitus. In one case of diabetes, exophthalmic goiter was associated; in the other, myxedema. The patients with exophthalmic goiter were examined systematically for spontaneous glycosuria and for the response of the blood sugar to injections of dextrose. By these means some abnormality was demonstrated in nearly all. Andersen concludes that in uncomplicated exophthalmic goiter the blood sugar during fasting is normal in most instances most of the time, but that an occasional higher than normal value during fasting is found in more than one half of the cases, and that the alimentary

blood sugar curve is increased in height and duration in most cases. Thyroidectomy is followed by a diminution in the abnormality of the alimentary blood sugar curve.

The renal threshold for dextrose in the patients with exophthalmic goiter may be slightly lower than normal, but typical renal glycosuria was not found in the patients studied. The threshold tended to rise after thyroidectomy. The patient with diabetes showed marked improvement in the diabetes following thyroidectomy, as has been repeatedly observed by other investigators in other patients.

Andersen inclines to the theory of Eppinger, Rudinger and Falta, which was later abandoned by Falta, that the thyroid directly inhibits the island mechanism of the pancreas and suggests that the thyroid product has a destructive effect on the island cells. An alternate theory, that was presented at various times by Allen, Fitz and Wilder, namely, that carbohydrate tolerance is depressed by elevation of the rate of metabolism in diabetic patients with hyperthyroidism, he rejects on the ground of old experiments of Freund and Marchand. These investigators, in 1913, reported that when the cervical medulla was severed in animals so that regulation of heat was obviated and the metabolism was increased up to 100 per cent, there was no demonstrable tendency to hyperglycemia; but it is scarcely necessary to point out that these experiments were not performed on diabetic animals, that the accuracy of determinations of basal metabolic rates made in 1913 may well be questioned and that fever and increased rates of chemical exchanges are by no means synonymous. It is not to be presumed, supposedly, that a dose of thyroid only large enough to bring the basal metabolic rate of a patient with myxedema up to normal would injure pancreatic cells. Yet in Andersen's patient with diabetes associated with myxedema the tolerance for carbohydrate was definitely depressed and the requirement of insulin correspondingly increased by doses of thyroid only large enough to raise the basal metabolic rate to normal.

The Compleat Pediatrician. By Wilburt C. Davison, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine, and Pediatrician, Duke Hospital; formerly Acting Head of Department of Pediatrics, the Johns Hopkins University School of Medicine, and Acting Pediatrician in Charge, the Johns Hopkins Hospital; Fellow, American Academy of Pediatrics and American College of Physicians; member, White House Conference, American Pediatric Society and American Board of Pediatrics. Cloth. Price, $3.75. Pp. 262. Durham, N. C.: Duke University Press, 1934.

This unique work is an index to the practice of pediatrics. The author has wisely and perhaps necessarily included in the book a list of instructions for its use. When one opens the book haphazardly, one is confronted by a mass of apparently unrelated words and symbols that become clear only after a perusal of these instructions.

Symptoms are set down, and each symptom is followed by a list of the diseases which may provoke it. The probable diseases are classified as very rare, rare, common and very common, and one is referred by a symbol to the portion of the book in which the disease itself is discussed.

The consideration of the diseases is confined to an outline of diagnosis and treatment.

There is a further section on preventive measures and one on infant feeding. A chapter is devoted to laboratory methods.

The book represents a tremendous amount of work and should be of definite value to the student and the general practitioner. Davison naïvely states that a large number of patients either recover or succumb, regardless of therapy, and his objective is to encourage the recognition of those conditions in which therapy is of value. He has succeeded in putting a tremendous amount of information into a small space. He is known to be an excellent pedatrician, and the title of his work would mark him as a fisherman, even if he had not included as his title an adaptation of Izaak Walton's "The Compleat Angler."

Das Beriberi Herz. By Prof. K. F. Wenckebach. Price, 12 marks. Pp. 106, with 38 illustrations. Berlin: Julius Springer, 1934.

This little monograph is the result of observations by Professor Wenckebach made in the Netherland Indies, and such a study of a controversial subject by an expert cardiologist seems to the reviewer of great value. Actual myocardial lesions are described, and an interesting tendency to "right-sided failure" is emphasized. The pathologic and clinical features are discussed in detail, and the text is richly illustrated with photographs of specimens, roentgenograms and electrocardiograms. There is a full bibliography.